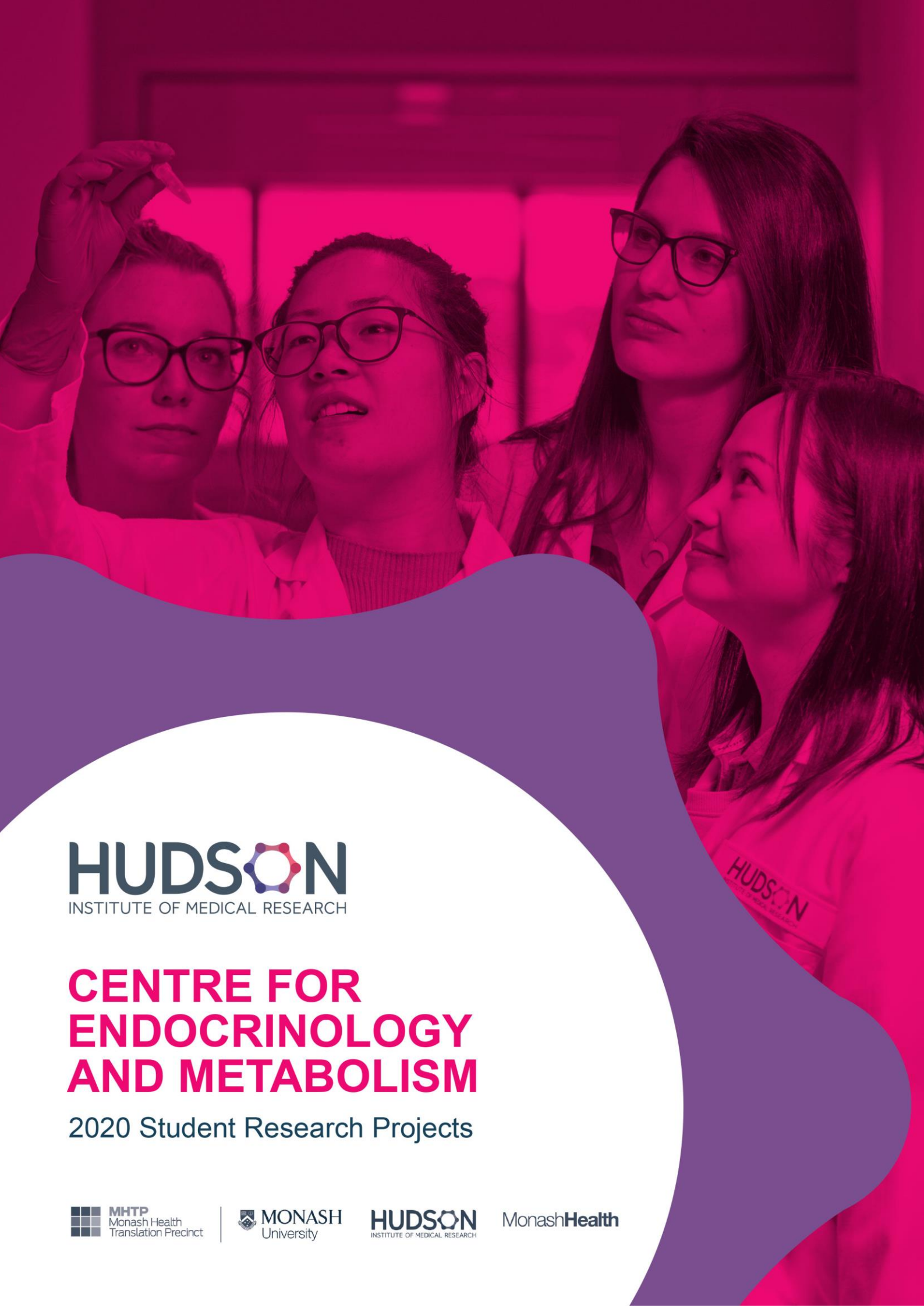




HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR ENDOCRINOLOGY AND METABOLISM

2020 Student Research Projects

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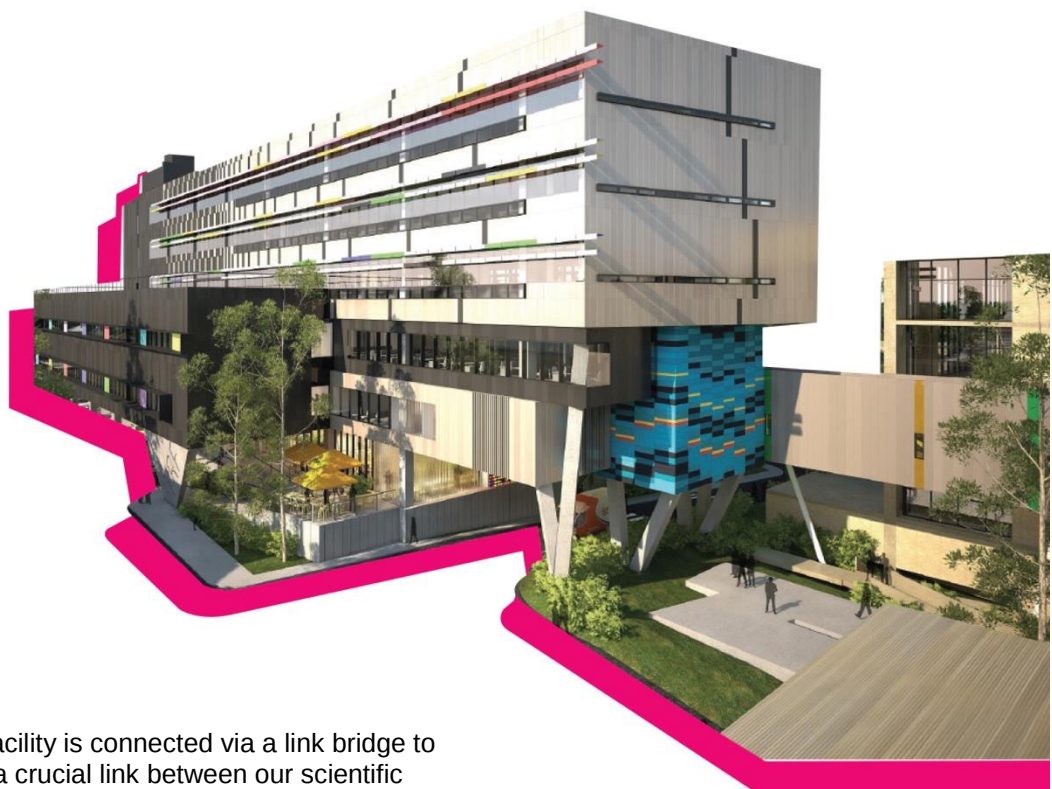
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The Translational Research Facility is connected via a link bridge to Monash Health, and provides a crucial link between our scientific discoveries and medical treatments. The facility houses nine world-leading technology platforms and an eight-bed,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

Welcome to Hudson Institute

Hudson Institute specialises in discoveries in four areas of medical need:

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

Our research discoveries have translational impact in:

- **Precision medicine**
- **Stem cell therapies**
- **Newborn health**
- **Rare diseases**
- **Hormone disorders**
- **Fertility**
- **Women's health**
- **Infection**
- **Chronic disease**

Our 475 scientists and students focus on laboratory discovery science, plus translational research – taking discoveries to patients and industry for real world impact.



296
STAFF



179
STUDENTS



50
RESEARCH
GROUPS



300
RESEARCH
PUBLICATIONS

Students at a glance in 2018



66
POSTGRADUATE
AND HONOURS
STUDENTS
COMPLETED



179
STUDENTS
138 PHD
2 MASTERS
39 HONOURS



25
STUDENTS
WITH MEDICAL
TRAINING

We educate and train nearly 180 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

- Gain exposure to university, institute and hospital research
- Attend national and international conferences
- Publish their research (74 student first author publications in 2018)
- Are mentored by leading supervisors and their teams
- Regularly win prestigious prizes and awards
- Have continuous opportunities for networking, learning and development

All work and no play ...

Hudson Institute is not all about work. Our students have the opportunity to join in a range of student networking and social events organised by the Hudson Institute Student Society (HISS).

Our precinct

Hudson Institute is a partner in the Monash Health Translation Precinct (MHTP), a major medical and scientific research hub at Monash Medical Centre in Clayton.

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

With our precinct partners, Monash University and Monash Health, our site brings together world-leading scientists, clinicians and educators to collaborate on innovative discoveries that advance human health.

Our Translational Research Facility (TRF) is connected to Monash Health via a walkway and provides a crucial link between our scientific discoveries and medical treatments.

The facility houses laboratories alongside nine state of the art technology platforms and an eight-bed, 21-chair Clinical Trials Centre supporting the transition of discoveries from initial Phase I testing to Phase IV primary health trials.



Centre for Endocrinology and Metabolism

Location:

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Centre Head:

Professor Peter Fuller AM

About the Centre:

The complex endocrine system impacts all aspects of health and disease. As the pre-eminent centre for endocrinology research originating from Prince Henry's Institute, laboratories in the Centre for Endocrinology and Metabolism at Hudson Institute of Medical Research undertake 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 obesity. Clinical translation of these findings to improve diagnosis, therapeutic intervention and prevention of disease remains a key focus for the Centre.



Research Groups and Heads



Brain and Gender

Dr Joohyung Lee



Cancer Drug Discovery

Associate Professor Colin Clyne



Cardiovascular Endocrinology

Dr Morag Young



Clinical Andrology

Professor Robert McLachlan AM



Hormone Cancer Therapeutics

Dr Simon Chu



Metabolic Bone Research

Associate Professor Frances Milat



Sex Determination and Gonadal Development

Professor Vincent Harley



Steroid Receptor Biology

Professor Peter Fuller AM



Cancer

Research Group: Cancer Drug Discovery

Nuclear receptor pharmacology

Suitability: Honours, Masters by Research, PhD

Project leaders: Associate Professor Colin Clyne;
Dr Chantal Magne Nde

e: colin.clyne@hudson.org.au

Project description: Anti-estrogen therapies, while very successful in the treatment of many breast cancers, are not effective for patients whose tumours do not express the estrogen receptor. Many patients who do respond to these drugs eventually become resistant to their effects. We are identifying alternative molecules related to the estrogen receptor (nuclear receptors) that could be exploited as novel breast cancer therapeutics. We have shown that one such receptor, LHR-1, induces cell proliferation, invasion and cancer stem cell-like phenotypes, making it an attractive target for cancer therapy development. We also recently demonstrated that LHR-1 interacts strongly with the estrogen biosynthetic pathway. To verify our findings and aid understanding of the role of LHR-1 in both the normal breast and breast cancer, we have developed a transgenic mouse model in which expression of human LHR-1 is directed specifically to the mammary gland. We have also shown that LHR-1 activity can be inhibited by peptides that block its interactions with co-regulator proteins, and are also currently using *in silico* and structural approaches to design small drug-like molecules that act in the same manner. Projects are available using both the animal model and *in vitro* pharmacology approaches.

Keywords: breast cancer, cancer, estrogen, nuclear receptors

Understanding resistance to breast cancer therapies

Suitability: Honours, Masters by Research, PhD

Project leaders: Associate Professor Colin Clyne;
Dr Chantal Magne Nde

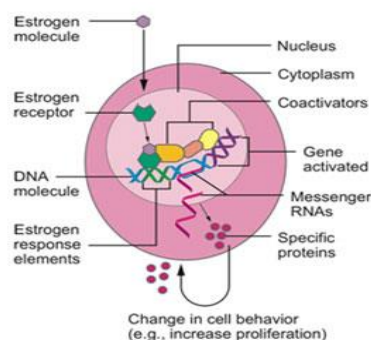
e: colin.clyne@hudson.org.au

Project description: Most breast cancer patients have tumours that require the female sex hormone estrogen to grow and develop. Blocking this action of estrogen (using drugs like tamoxifen) is a commonly used and effective therapy. However, many patients

develop resistance to these drugs, leading to disease recurrence with poor prognosis. Understanding how therapeutic resistance occurs is therefore critical for the development of more effective therapies. We have identified a novel protein (of unknown function) that becomes activated in breast cancers that have developed resistance to tamoxifen. We have shown that this protein amplifies the effects of estrogen, making breast cancer cells more responsive to the hormone, and increasing their ability to divide and spread. This effect may make cells less responsive to tamoxifen, thereby contributing to the development of resistance. This project aims to:

- understand how this protein modulates estrogen action at the molecular level; and
- determine its potential as a marker to identify patients who may not respond well to tamoxifen.

Keywords: breast cancer, cancer, endocrinology, estrogen, nuclear receptors



Research Group: Hormone Cancer Therapeutics

Molecular pathogenesis of granulosa cell tumours of the ovary

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Simon Chu; Professor Peter Fuller

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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. 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

analyses and microRNA analyses. Other studies explore the role of nuclear receptors including estrogen receptor-beta (ERbeta) and PPARgamma, and of genes that we have identified as being overexpressed in advanced disease with a view to developing novel therapeutic strategies.

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

Role of XIAP in endocrine cancer (ovarian and thyroid)

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr 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 elevated expression in human cancers, XIAP has become an attractive therapeutic target for novel anti-cancer treatment. Small-molecule inhibitors are in various stages of development, from preclinical to phase II clinical trials. XIAP has an important role in both ovarian cancer and thyroid cancer. 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.

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

Elucidating novel functions of MAGMAS signalling in ovarian cancer progression and chemoresistance

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Simon Chu; Professor Nuzhat Ahmed; Professor George Kannourakis

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Project description: Ovarian cancer is asymptomatic and there are no sensitive and specific markers to detect it at an early stage. The 75% of women (more than 900 Australian women per year) diagnosed with stage III/IV

disease have a survival rate of less than 30% for five years. The development of recurrent peritoneal metastases after standard chemotherapy treatment is a major clinical issue in the management of ovarian cancer patients. Hence, there is an urgent need to identify molecules that can be manipulated in conjunction with chemotherapy treatment for better outcomes for ovarian cancer patients. Mitochondria are key organelles in many metabolic and biosynthetic pathways, and the adaptation of cancer cells towards mitochondrial function is crucial during neoplastic transformation. Genes encoding mitochondrial proteins have shown encouraging results as potential therapeutic targets for cancer. Our laboratory has recently identified novel expression of MAGMAS (mitochondria-associated granulocyte macrophage colony stimulating factor signalling molecule) in ovarian tumours. MAGMAS, also referred to as PAM16, was previously described as a mitochondria-associated protein, involved in pre-protein import into mitochondria and essential for cell growth and development. The protein also has an important role in controlling oxidative damage. Hence, the expression of MAGMAS, which is significantly elevated in advanced-stage ovarian tumours compared to benign ovarian tumours, warrants further investigation. This study is based on the hypothesis that MAGMAS, through its inherent ability to regulate cell growth and oxidative stress, is directly responsible for driving ovarian tumourigenesis at the primary tumour site, within the ascites fluid, and subsequent ongoing disease progression in ovarian cancer patients after chemotherapy treatment. This study therefore aims to investigate the role of MAGMAS in ovarian cancer progression, metastasis and chemoresistance-associated recurrence.

Keywords: cancer, ovarian cancer, mitochondria, mitochondria-associated granulocyte macrophage colony stimulating factor, molecular biology, CRISPR, xenografts



Cardiovascular Pathology

Research Group: Cardiovascular Endocrinology

A search for new biomarkers and therapeutic targets in heart failure

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Morag Young; Dr Jun Yang

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Project description: Heart failure occurs when the heart muscle weakens and is unable to pump enough blood to meet the body's needs. It is a major public health issue, affecting 30,000 patients each year in Australia. Recent research shows that the hormone receptor, the mineralocorticoid receptor (MR), may play a key role in cardiac fibrosis, which stiffens the heart tissue, by activating macrophages/monocytes.

We propose to use this new information to identify biomarkers in patients with heart failure that can be used to diagnose those patients with heart failure who would benefit from MR blocking therapy, and also to monitor the efficacy of treatments without the need for expensive tests in the clinic (i.e. cardiac MRI, cardiac CT). There is no simple blood test to diagnose heart failure. By studying circulating blood cells in patients with heart failure or primary aldosteronism, an endocrine cause of hypertension, before and after they are treated with MR blockers, this research hopes to detect tell-tale blood markers that indicate early heart failure and predict response to treatment. These markers may also be suitable therapeutic targets for new heart failure drugs which do not cause kidney-related side effects. Data generated in this project will be used to create a routine clinical test that in the future will help to profile patient responses to treatment to guide clinical decision-making in heart failure clinics. This project will lay the



crucial foundation and proof-of-concept that a unique biomarker signature can determine patient responses to MR therapy.

Keywords: mineralocorticoid receptor, macrophage, heart failure

Mineralocorticoid receptor signalling pathways in macrophages; new mechanisms of heart disease

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Morag Young; Professor Peter Fuller

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Project description: The global importance of addressing cardiovascular disease and hypertension cannot be overestimated; this field needs new insights and novel strategies. The mineralocorticoid receptor (MR) is classically associated with the regulation of sodium, potassium, fluid balance and blood pressure control. It is also present in various non-epithelial cell types including cardiac myocytes, vascular smooth muscle cells, brain cells and immune cells such as macrophages. In these cells, the actions of the MR are not completely characterised but in many cases do not relate to salt or fluid regulation. At present, the cascade of events leading to MR activation and how MR activation results in inflammation and fibrosis are not clearly defined. In animal models, cardiac fibrosis is exacerbated by mineralocorticoid/salt administration but attenuated by receptor blockade and absent in mice specifically lacking cardiac myocyte MR or macrophage MR. Previous data from this laboratory demonstrate a critical role for MR signalling in the monocyte/macrophage lineage, a cell type in which the role of MR signalling is poorly defined. The recent identification of the cardio-protective effects of macrophage-specific deletion of the MR is an exciting advance in our understanding of disease processes and highlights new therapeutic targets that could lead to new treatments for the treatment of cardiac failure and hypertension that are specifically designed for macrophages. The goal of this project is to identify novel pathways using novel proteomic and genomic screening technologies and to define and characterise these pathways using transgenic models and clinical samples. In this way, we hope to identify novel mechanisms of heart disease, determine the optimal way to treat patients and avoid the serious side effects of current treatments.

Keywords: heart disease, mineralocorticoid receptor, macrophage, cardiac fibrosis

Nuclear receptor co-regulators in heart disease and inflammation; new targets for fine-tuning receptor actions in health and disease

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Morag Young; Associate Professor Colin Clyne

e: morag.young@hudson.org.au

Project description: Nuclear receptors associate with co-regulatory proteins in order to modulate gene transcription: These co-regulators can have profound effects on receptor activity and may be targeted therapeutically for the treatment of a range of diseases. We have identified novel mineralocorticoid receptor (MR) co-regulators from the heart and kidney and this project will characterise their activity in heart and kidney cells and other cell-based models as appropriate, to identify the molecular mechanisms of their activity. A separate project involves a T7 phage screen to identify novel MR co-regulators in macrophages, validation as true co-regulators and characterisation of their activity in immune cells, and is more suited to a PhD applicant. This project will include a suite of molecular biology techniques, cell culture, western blotting and RT-PCR.

Keywords: steroid hormone receptor signalling, endocrine

The role of human amnion epithelial cell-derived exosomes in modulating cardiac fibrosis in mice

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Morag Young; Associate Professor Rebecca Lim

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Project description: The cost of treating heart failure in Australia is > \$3 billion per year (NHF). Heart failure occurs when the heart is unable to pump sufficient blood due to 'stiffening' of the myocardium caused by increased tissue fibrosis and changes in myocardial passive stiffness. Therapy directed towards cardiac fibrosis could reduce the progression of heart failure. We aim to use exosomes derived from human amnion epithelial cells (HAECs) as a therapeutic treatment in reducing cardiac fibrosis. Exosomes are small vesicles (~50-150 nm in diameter) secreted by cells. They have the ability to facilitate the uptake of therapeutic proteins or RNAs into injured cells and use them for healing purposes. The packaging of exosomes depends on the cell type. Exosomes

released from HAECs are safe to be used for curing diseases.

This study will investigate the effect of exosomes derived from HAECs in an experimental setting of cardiac fibrosis in mice: the deoxycorticosterone (DOC)/salt-mediated cardiac fibrosis mouse model. DOC activates the mineralocorticoid receptor (MR) in the heart and promotes cardiac fibrosis. This model is characterised by an inflammatory response detectable from 8 days and fibrosis which is detectable from 3 weeks; at 8 weeks tissue fibrosis and hypertension are established. Cardiac function (reduced ejection fraction and diastolic relaxation) is also impacted. This project will involve *in vivo* and *in vitro* studies designed to evaluate the impact of exosomes on cardiac tissue remodelling and function. Techniques involved include cell proliferation and migration assays, exosome phenotyping, analysis of cardiac hypertension and fibrosis in mice, and analysis of the disease phenotype at the histological and molecular level.

Keywords: exosome, cardiac fibrosis



It's about time: How does the mineralocorticoid receptor regulate cardiomyocyte function in heart disease and in biology?

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Morag Young; Professor Peter Fuller

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Project description: This project will involve molecular and immunohistochemical analyses of hearts, aortas and kidneys from transgenic mice generated by a specific breeding program and subject to treatment that causes heart failure. It will address the novel mechanisms that have been identified in previous work. These studies identified a number of attractive candidate downstream signalling pathways that we will directly investigate using *in vivo* and *in vitro* models to determine their regulation by the mineralocorticoid receptor (MR) and their

specific role in the development of heart failure. The goal of projects undertaken in this topic is to identify novel therapeutic targets for a broad range of cardiovascular diseases that are cardiac-selective, and thus have fewer side effects associated with MR actions in other tissues and organs. In addition to *in vivo*

monitoring of animal disease models, techniques will include immunohistochemistry, cell culture, western blotting and RT-PCR techniques.

Keywords: cardiomyocyte, mineralocorticoid receptor, hormone, cardiac fibrosis, circadian clock

Endocrinology and Metabolism

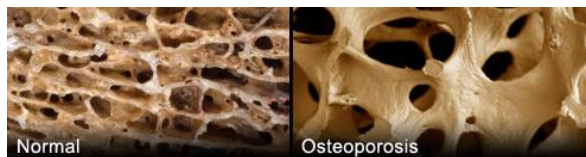
Research Group: Metabolic Bone Research

Osteoporosis and metabolic bone disorders

Suitability: BMedSci, PhD

Project leader: Associate Professor Frances Milat
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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.



Research Group: Cardiovascular Endocrinology

Macrophage mineralocorticoid receptor signalling regulation of adipose tissue inflammation and glucose tolerance

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Morag Young; Professor Peter Fuller

e: morag.young@hudson.org.au

Project description: Mineralocorticoid receptors (MR) play a pivotal role in regulating the macrophage inflammatory phenotype. Targeting the MR in macrophages using gene targeting in mice prevents inflammation and fibrosis in a range of diseases. We have preliminary data to show that mice lacking the MR in macrophages are protected from glucose intolerance due to obesity. This project aims to identify the mechanisms of the protective effect by studying metabolic changes in fat, muscle

and liver. This project will involve immunohistochemistry, high throughput RT-PCR platforms, database analysis, western blotting and cell culture techniques.

Keywords: obesity, brown fat, macrophages

Evaluating the prevalence of primary aldosteronism in patients with stroke and/or atrial fibrillation

Suitability: BMedSci, Masters by Research, PhD

Project leader: Dr Jun Yang, Dr Ben Clissold
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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. In particular, PA confers a 3-4 fold increase in the risk of stroke and atrial fibrillation compared to essential hypertension in blood pressure-matched patients. However, PA screening is not actively recommended in stroke/atrial fibrillation (AF) management guidelines. Given the potential health impact of diagnosing a potentially curable form of hypertension, and reducing the risk of stroke and AF, we seek to evaluate the prevalence of PA in patients presenting to Monash Health with either acute stroke or transient ischemic attack. This project has the potential to change management guidelines for hypertension in stroke patients and optimise the timely diagnosis of PA.

Keywords: primary aldosteronism, stroke, TIA, hypertension, endocrine hypertension, aldosterone

Evaluating the cost-effectiveness of screening for PA in all versus subgroups of hypertensive patients

Suitability: BMedSci, Masters by Research, PhD

Project leader: Dr Jun Yang; Associate Professor Gang Chen

e: jun.yang@hudson.org.au

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. However, without a formal cost analysis, hypertension screening 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 aldosterone-renin ratio (ARR) to screen for PA in primary care versus no screening. The within-trial analysis will be extrapolated using a Markov model, consisting of health outcomes following screening procedures versus no screening, to capture the long-term cost. The quality of life and direct medical costs will be collected from a current trial. 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. Sensitivity analysis will be performed to evaluate the cost-effectiveness of ARR screening in all versus subgroups of hypertensive patients. The outcomes will directly influence policy.

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



Identification of novel transcriptomic markers of PA

Suitability: Honours, BMedSci, Masters by Research, PhD

Project leader: Dr Jun Yang; Dr Morag Young

e: jun.yang@hudson.org.au

Project description: Whilst dichotomous thresholds are currently used to diagnose primary aldosteronism (PA), emerging data supports the concept of a continuum of aldosterone excess. A longitudinal cohort study showed that higher aldosterone in the setting of a suppressed renin level (392 of 850 normotensive patients) was significantly associated with the development of hypertension. 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.

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

Establishment of a national primary aldosteronism registry to enable comprehensive data collection

Suitability: Masters by Research

Project leader: Dr Jun Yang

e: jun.yang@hudson.org.au

Project description: Clinical registries play an important role in measuring healthcare delivery, supporting quality improvement and evaluating clinical outcomes, particularly in the long-term. There are no primary aldosteronism (PA) registries in Australia. This is in contrast to other countries which lead the research in PA, including China (CONPASS PA Study Group - 3 publications in leading endocrine journals in 2018), Japan (JPAS - 6), Taiwan (TAIPAI - 8) and Germany (German Conn's Registry - 10). Based on our existing REDCap database, we will develop a multicenter registry to systematically collect comorbidities, diagnostic parameters and long-term outcomes of patients with PA, both in and outside of clinical trials.

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

Research Group: Steroid Receptor Biology

Structure-function relationships of the mineralocorticoid receptor

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Peter Fuller

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Project description: The mineralocorticoid receptor (MR) is an important therapeutic target in cardiovascular disease. We have identified interactions of the receptor that differ between the physiological hormones, aldosterone and cortisol. 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 yeast 2-hybrid screens, transactivation assays, structural analysis, mutation detection, comparative biology and a series of unique transgenic mouse models in which the MR has been either mutated or knocked-out. This work is also associated with our clinical program.

Keywords: aldosterone, mineralocorticoid, receptor, adrenal

Research Group: Clinical Andrology

Translational studies in male infertility

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Robert McLachlan

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Project description: Male infertility is a leading cause of human infertility and solely or partly accounts for half of all Assisted Reproduction Technologies (ART) procedures. The bulk of cases are unexplained but a genetic basis for many cases is suspected. Only 10% can be

explained by disorders of chromosomal number or structure, Y chromosome deletions or a few specific gene defects. We have accumulated a repository of genomic DNA and clinical information from over 2000 infertile men, their partners and their ART-conceived children for use in genetic studies. This repository is being used to identify genetic causes of male infertility. Specific research areas include assessment for mutations in genes involved in DNA repair and sperm tail development and the involvement of small non-coding RNAs in sperm development and function. This research also focuses on the importance of genetic instability and epigenetic imprinting in male infertility. Studies on the genetic basis of male infertility are aimed at leading to better diagnostic tests and treatment for infertile couples and to aiding in understanding the impact of ART on the health of the next generation.

Keywords: infertility, ART, sperm development



Genetic Diseases

Research Group: Sex Determination and Gonadal Development

ATR-X syndrome and gonadal development

Suitability: Honours, Masters by Research, PhD

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 disorders of sex development (DSD) 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.

Keywords: sex determination, ATRX syndrome, human genetics, disorders of sex development

Characterisation of novel gonadal targets of Sox9

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Vincent Harley

e: vincent.harley@hudson.org.au

Project description: For the majority of disorders of sex development (DSD) 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 mutated in DSD 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 testis 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 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.

Keywords: sex determination, *Sox9*, disorders of sex development, molecular genetics, sex differences

FGF signalling and sex reversal

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Vincent Harley

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Project description: We have identified the first *FGFR2* mutations in XY female sex-reversed disorders of sex development (DSD) patients. One case, 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 patients. We will use our 'knockin' *Fgfr2c*C342Y and 'knockout' *Fgfr2c*^{-/-} mouse models to understand the role of *FGFR2* in testis determination and disease and to identify *FGFR2*-regulated genes and signalling pathways which might be defective in DSD patients. 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.

Keywords: *FGFR2*, sex determination, sex reversal, disorders of sex development, mouse models



Identifying the genes responsible for disorders of sex development (DSD)

Suitability: Honours, PhD

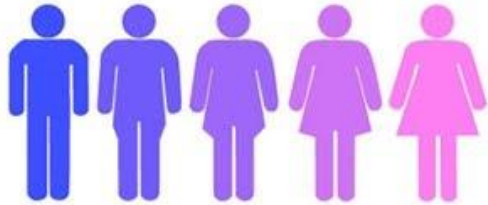
Project leader: Professor Vincent Harley

e: vincent.harley@hudson.org.au

Project description: Disorders of sex development (DSDs), formerly intersex, are congenital conditions where gonadal or anatomical sex is atypical. DSDs encompass a wide range of abnormalities, including hypospadias (abnormal urinary opening in males), gonadal dysgenesis (underdeveloped or imperfectly formed gonads) and ambiguous genitalia and sex reversal (i.e. XX males and XY females). Our aim is to identify genes causing DSDs, 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 DSDs. Approaches include human genetics, as well as molecular, cell and developmental biology. See: Ono M. and Harley V. (2013) Disorders of sex development: new genes, new concepts. *Nature Reviews Endocrinology* 9:79-91; visit website on NHMRC Program on DSDs: <http://dsdgenetics.org/>.

Keywords: sex determination, genes, human genetics, disorders of sex development



The biological basis of gender identity

Suitability: Honours, PhD

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 or postnatal social determinants. We are investigating the role of genes in patients with gender identity disorders. This project involves undertaking genetic association studies in the world's largest cohort of male-to-female transsexuals. It focuses upon genes involved in sex hormone synthesis and signalling.

Keywords: gender identity, gene associations, sex hormones

Neuroscience and Psychiatry

Research Group: Brain and Gender

Biological basis of sex differences in the healthy and diseased brain

Suitability: Graduate Diploma, Short Projects, Honours, Masters by Research, PhD

Project leaders: Dr Joohyung Lee; Dr Rachel Hill
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Project description: Exploring sex differences in the brain is important for their impact and therapeutic implications for many neurodegenerative and psychiatric diseases. For instance, females suffer more from mood disorders such as depression and anxiety, whereas males are more susceptible to Parkinson's disease (PD), attention-deficit hyperactivity disorder (ADHD), schizophrenia and autism. Better understanding of the biology underlying brain sex differences will be vital for designing novel therapeutic agents that will have optimal effectiveness in each sex. The current project will investigate the contribution of sex-specific genes (i.e. X and Y chromosome genes) and/or sex hormones (e.g. estrogen) on sex differences in neurodegenerative disorders such as PD and psychiatric disorders such as ADHD, schizophrenia and autism. Approaches include animal models of neurodegenerative and psychiatric diseases, stereotaxic neurosurgery, intracerebral drug administration, assessment of rodent behaviour neuroscience, neuroanatomy, qRT-PCR, immunohistochemistry and electrophysiology.

Keywords: autism, ADHD, Parkinson's disease, schizophrenia, dopamine, sex differences, *SRY*, extreme male brain theory

De-masculinising the male brain

Suitability: Graduate Diploma, Short Projects, Honours, Masters by Research, PhD

Project leader: Dr Joohyung Lee
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Project description: The Y chromosome gene, *SRY*, is widely expressed in the male brain, such as in the substantia nigra, ventral tegmental area (VTA), pre-frontal cortex (PFC) and hippocampus. These brain regions, which control important functions such as goal-

directed actions, attention, and learning and memory, are also sexually dimorphic. This project seeks to determine the relative contribution of *SRY* to the sex differences in the anatomy, biochemistry and physiology of these brain regions. We will assess the consequence of reducing *SRY* levels in these brain regions, via site-specific injection of *SRY* antisense oligonucleotide, on behaviour (i.e. attention, memory and goal-directed behaviours), neurochemistry (i.e. measurement of catecholamine levels and cell numbers), and gene expression (RNAseq, ChIPseq).

Keywords: *SRY*, brain sex differences, Y chromosome, spatial memory, attention, emotional learning, reward and addiction



Is deep brain stimulation neuroprotective in Parkinson's disease?

Suitability: Graduate Diploma, Short Projects, Honours, Masters by Research, PhD

Project leaders: Dr Joohyung Lee; Professor Dominic Thyagarajan
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Project description: Parkinson's disease (PD) is a debilitating neurological disorder, primarily associated with inability to initiate and control voluntary movement. These symptoms result from the loss of brain cells that produce a chemical called dopamine, which acts as a signal to initiate movement. Current PD therapies only treat the symptoms but do not halt or slow the dopamine cell loss. Aside from medications, deep brain stimulation (DBS) is a highly effective therapy for the symptoms of PD. DBS is a relatively safe procedure that uses a surgically implanted, battery-operated medical device called a neurostimulator (like a heart pacemaker) to deliver electrical stimulation to targeted areas in the brain that control movement, blocking the abnormal nerve signals that cause PD symptoms. Over the last few decades, DBS has been shown to provide remarkable therapeutic effect on carefully selected patients including improvement of

daily tasks and therefore quality of life. Whilst recent clinical and animal studies have hinted that DBS may also slow the progression of the disease in PD, the findings are inconclusive due to the inadequate patient sample size and limitations of the animal models used. In the current proposal, we will determine whether DBS can slow or halt the disease progression in a clinically relevant animal model of PD. Successful completion of this proof-of-concept study will provide essential steps toward finally developing a treatment that slows this relentlessly progressive and disabling illness.

Keywords: Parkinson's disease, deep brain stimulation, neuroprotection, subthalamic nucleus

Novel therapeutic targets for Parkinson's disease

Suitability: Graduate Diploma, Short Projects, Honours, Masters by Research, PhD

Project leaders: Dr Joohyung Lee; Professor Dominic Thyagarajan

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Project description: Parkinson's disease (PD) is a debilitating neurodegenerative disorder that affects over 7 million people worldwide. The hallmark symptom of PD is the inability to initiate and maintain voluntary movement, which results from the loss of midbrain dopamine neurons. Current PD therapies (e.g. levodopa) only relieve the symptoms but do not modify the disease progression. The current project aims to identify and characterise (i) novel therapeutic targets to slow or halt the progression of PD and (ii) novel sex-specific targets for neuroprotection or symptomatic relief in PD. Approaches include toxin- and genetic-based animal models of PD, stereotaxic neurosurgery, intracerebral drug administration, assessment of rodent behaviour, analysis of post-mortem PD patient brain tissue, neuroanatomy, qRT-PCR, immunohistochemistry and electrophysiology.

Keywords: dopamine, substantia nigra, neuroprotection, pre-symptomatic, Sry, neurotransmitter

Why are boys more susceptible to attention-deficit hyperactive disorder (ADHD) than girls?

Suitability: Graduate Diploma, Short Projects, Honours, Masters by Research, PhD

Project leaders: Dr Joohyung Lee; Dr Rachel Hill; Dr Xin Du

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Project description: Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric disorder in children, consisting of age-inappropriate symptoms of inattention, hyperactivity and impulsivity. Whilst the exact cause is unknown, it is clear that ADHD is much more common in boys than girls with a ratio of 4:1. We hypothesise that the male specific Y chromosome gene *SRY* is a factor involved in the susceptibility of boys to ADHD. This project seeks to determine whether (i) *SRY* levels are dysregulated in human and animal models of ADHD and (ii) reducing *SRY* levels can attenuate the symptoms of ADHD in males, using a well-established rodent model of ADHD. Approaches include animal models of ADHD, neurosurgery, behavioural neuroscience (memory and attentional behaviours, locomotion, anxiety), neuroanatomy, and cellular and biology techniques (qRT-PCR, RNAseq).

Keywords: *SRY*, attention, dopamine, brain sex differences, sex chromosomes, pre-frontal cortex, hippocampus

Research Group: Sex Determination and Gonadal Development

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

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Vincent Harley

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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.

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

How are male and female brains different?

Suitability: Honours, PhD

Project leader: Professor Vincent Harley

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Project description: Male and female brains differ in anatomy, chemistry and behaviour. 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.

Keywords: SRY, brain differences, sex differences



Reproduction and Development

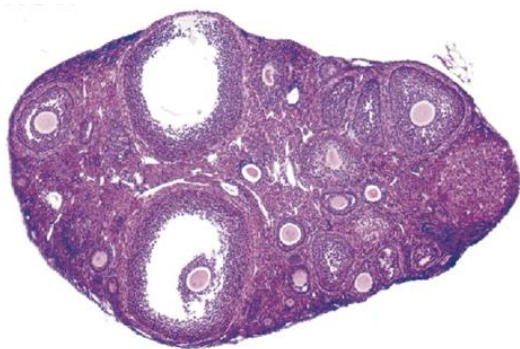
Research Group: Hormone Cancer Therapeutics

Role of XIAP in normal ovarian folliculogenesis

Suitability: Honours, Masters by Research, PhD

Project leaders: Dr Simon Chu; Professor Peter Fuller; Professor John Silke

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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.

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

Research Group: Steroid Receptor Biology

Mineralocorticoid receptor regulation of gene expression in reproductive tissue

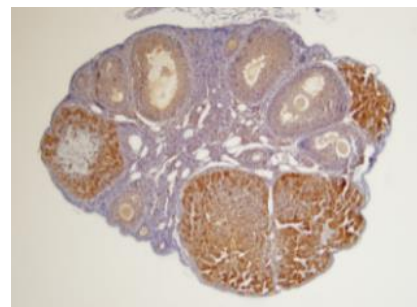
Suitability: Honours, Masters by Research, PhD

Project leader: Professor Peter Fuller

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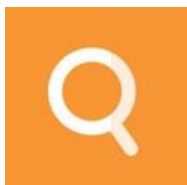
Project description: The mineralocorticoid receptor (MR) is best known for its involvement in the regulation of salt and water balance. However, non-classical tissues have been identified as expressing MR, giving rise to the hypothesis that the MR also plays a regulatory role in these tissues. We have 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. We have created a tissue-specific knockout mouse to investigate the impact of MR loss on mammary and ovarian tissue development and function. 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.

Keywords: mineralocorticoid, mammary tissue, knockout



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