HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR ENDOCRINOLOGY AND METABOLISM

2022 Student Research Projects

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

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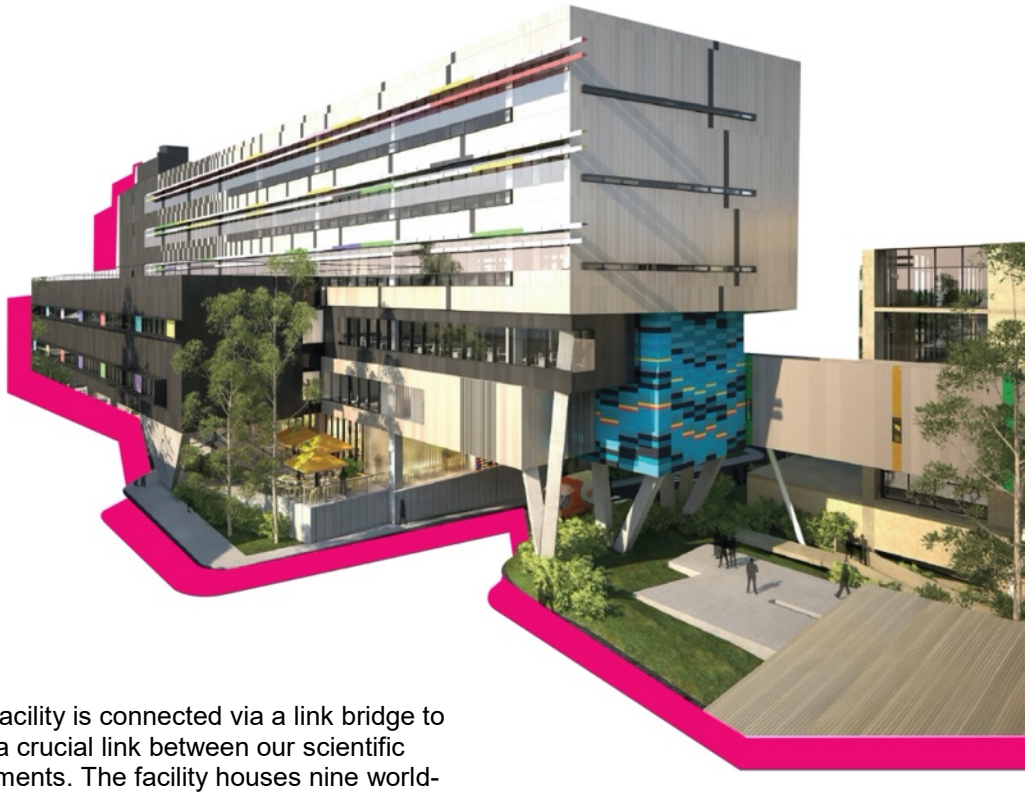


The Translational Research Facility is connected via a link bridge to Monash Health and provides a crucial link between our scientific discoveries and medical treatments. The facility houses nine world-leading technology platforms and an eight-bed, 21-chair Clinical Trials Centre that support the transition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

Welcome to Hudson Institute

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

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

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

285 STAFF

158 STUDENTS

43 RESEARCH GROUPS

285 RESEARCH PUBLICATIONS

Students at a glance 2020

60 POSTGRADUATE AND HONOURS STUDENTS COMPLETED

158 STUDENTS 113 PHD 6 MASTERS 38 HONOURS

31 STUDENTS WITH MEDICAL TRAINING

We educate and train more than 150 students through our academic affiliation with Monash University and other tertiary institutions. 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 (there were 41 student first author publications in 2020)
- Are mentored by leading supervisors and their teams
- Regularly win prestigious prizes and awards
- Take part in regular networking, and learning and development programs.

All work and no play…

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

Our precinct

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

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

We are a founding member of the Monash Health Translation Precinct 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 rapidly transitioned into practical treatments.

Working alongside clinicians in Melbourne hospitals for over 50 years, our scientists pioneered IVF, discovered the hormone inhibin and revolutionised the treatment of endocrine disorders. They are now leading developments in cell therapies, endocrinology, paediatric cancer and the human microbiome. Our worldwide scientific and medical collaborations provide a foundation for transformative healthcare programs across the globe.

Centre for Endocrinology and Metabolism

Location

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

t: +61 3 8572 2534

e: francine.brennan@hudson.org.au

w: hudson.org.au/research-centre/centre-for-endocrinology-and-metabolism/

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 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 Leaders

Cancer Drug Discovery
Associate Professor Colin Clyne
PhD

Clinical Andrology
Professor Robert McLachlan AM
MBBS PhD FRACP

Endocrine Hypertension
Dr Jun Yang
MBBS PhD FRACP

Hormone Cancer Therapeutics
Dr 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 the prevalence of primary aldosterone in patients with stroke and/or atrial fibrillation

Suitability: BMedSci, Masters by Research, PhD

Project leaders: Dr Jun Yang, Dr Ben Clissold

Email: 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. 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 different strategies for the diagnosis and management of primary aldosteronism

Suitability: BMedSci, Masters by Research, PhD

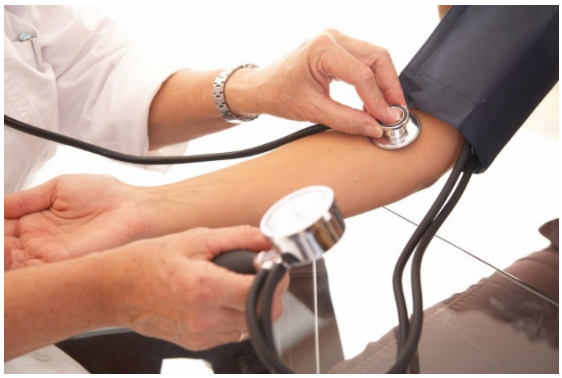
Project leaders: Dr Jun Yang, Associate Professor Gang Chen

Email: 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. 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.

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

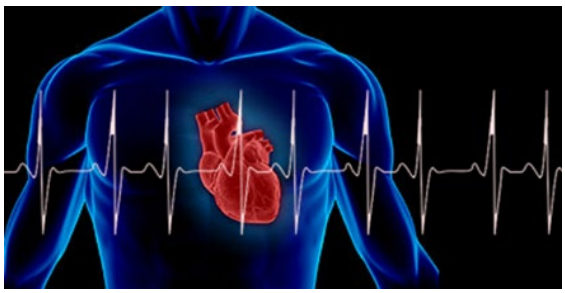
Project leaders: Dr Jun Yang, Associate Professor Morag Young

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 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



Impact of ethnicity on the prevalence and aetiology of hypertension

Suitability: BMedSci, Masters by Research, PhD

Project leaders: Dr Jun Yang, Dr StellaMay Gwini

Email: jun.yang@hudson.org.au

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, salt-sensitive 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. Given the multicultural composition of Australian society, we are perfectly positioned to examine the prevalence and aetiology of hypertension in ethnically diverse groups so as to develop the most effective diagnostic and treatment approaches for the control of their hypertension.

Keywords: primary aldosteronism, hypertension, endocrine hypertension, ethnicity

Exploring endocrine hypertension in Indigenous populations

Suitability: BMedSci, Masters by Research, PhD

Project leader: Dr Jun Yang

Email: jun.yang@hudson.org.au

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 in Victoria to gauge their attitude towards hypertension diagnosis and treatment, and seek their input in exploring primary aldosteronism in their communities.

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

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

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. 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 the telomerase gene, 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 normal ovarian folliculogenesis

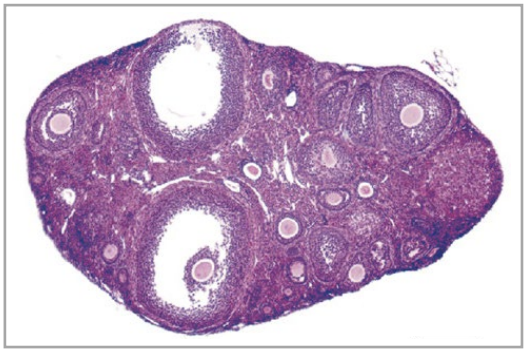
Suitability: Honours, Masters by Research, PhD

Project leaders: Dr 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.

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



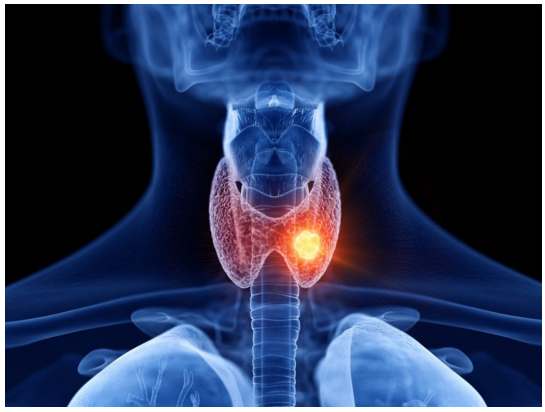
Role of XIAP in endocrine cancer (ovarian and thyroid)

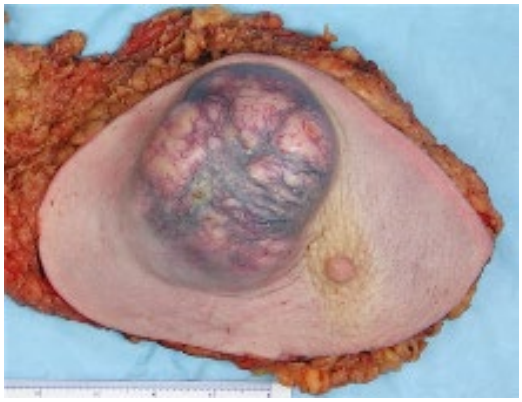
Suitability: Honours, Masters by Research, PhD

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

Email: simon.chu@hudson.org.au

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.

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

Metabolic Bone Research

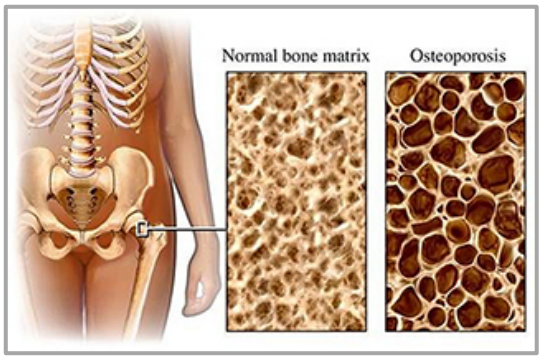
Osteoporosis and metabolic bone disorders

Suitability: BMedSc, PhD

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.

Sex Development

Characterisation of novel gonadal targets of *Sox9*

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Vincent Harley

Email: 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 are 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 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.

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

ATR-X syndrome and gonadal development

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

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

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

Suitability: Honours, PhD

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

Project description: Disorders of sex development (DSDs), formerly known as 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), 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 the website for the NHMRC Program on DSDs: http://dsdgenetics.org/.

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

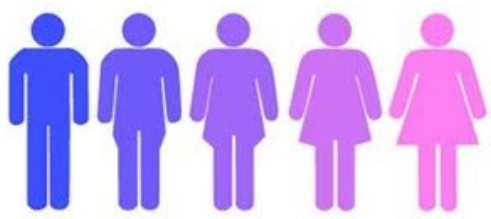
The biological basis of gender identity

Suitability: Honours, PhD

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

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

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

Suitability: Honours, Masters by Research, PhD

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.

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

How are male and female brains different?

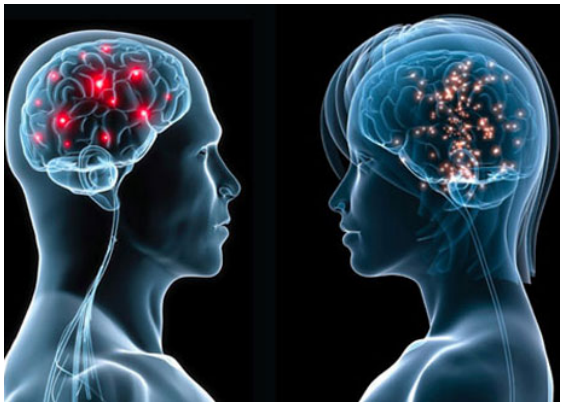
Suitability: Honours, PhD

Project leader: Professor Vincent Harley

Email: vincent.harley@hudson.org.au

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



Steroid Receptor Biology

Structure-function relationships of the mineralocorticoid receptor

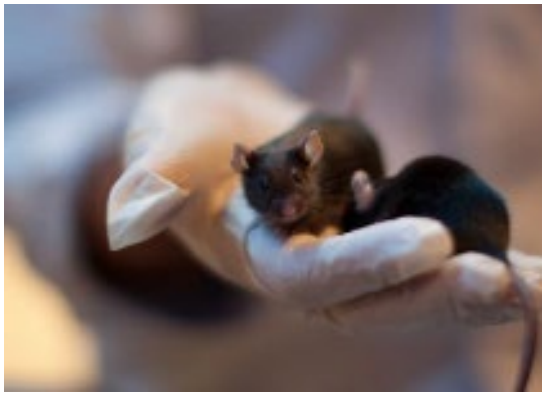
Suitability: Honours, Masters by Research, PhD

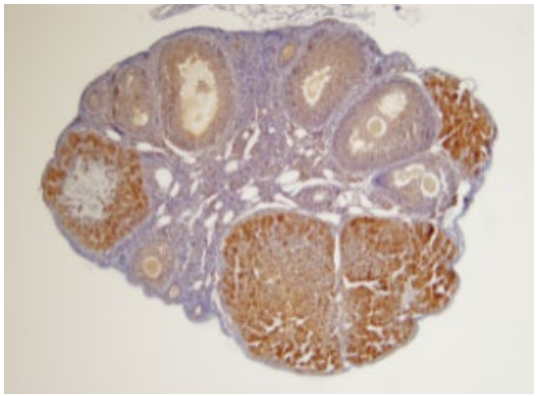
Project leader: Professor Peter Fuller

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 has been either mutated or knocked-out. This work is also associated with our clinical program.

Keywords: aldosterone, mineralocorticoid, receptor, adrenal





Mineralocorticoid receptor regulation of gene expression in reproductive tissue

Suitability: Honours, Masters by Research, PhD

Project leader: Professor Peter Fuller, Dr 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.

Keywords: mineralocorticoid, mammary tissue, knockout

Contact our supervisors

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

STEP 1: Find a project you are interested in from this book or at hudson.org.au/research-centre/centre-for-endocrinology-and-metabolism/.

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

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

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

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HUDSON INSTITUTE OF MEDICAL RESEARCH

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