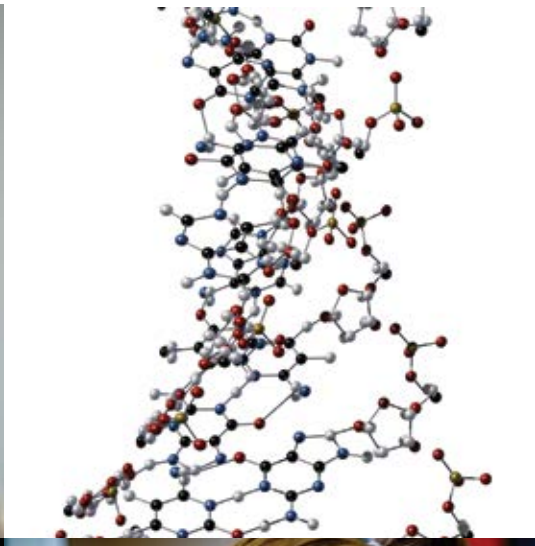
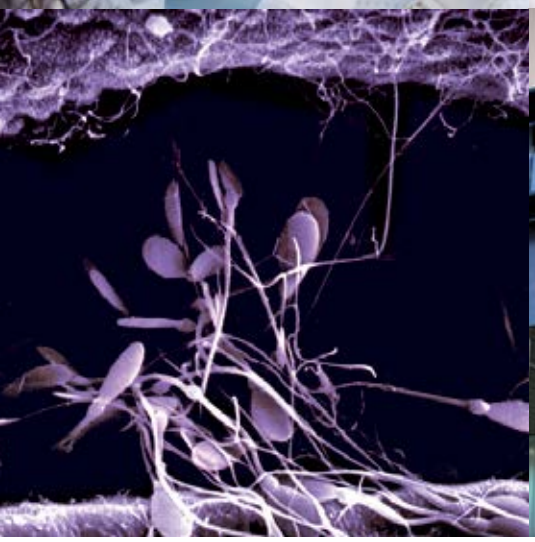
HUDSON
INSTITUTE OF MEDICAL RESEARCH



Student Research Projects 2017

www.hudson.org.au

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For more information please visit
our website:
HUDSON.ORG.AU

https://www.facebook.com/hudson.org.au

https://twitter.com/Hudson_Research

STUDENT RESEARCH PROJECTS 2017

www.hudson.org.au

Contents

"We are taking ground-breaking discovery research into patient care faster than ever before."

Professor Bryan Williams
Director, Hudson Institute of Medical research
Distinguished researcher and international authority on innate immunity and cancer biology.
Research Group: Cancer and Innate Immunity

Professor Bryan Williams with three-year-old cancer patient Elizabelth
PICTURE: SUSAN WINDMILLER, NEWSPIX

Advancing Health Care

The state-of-the-art six-storey MHTP Translational Research Facility opened in 2015, bringing together researchers, postgraduate students, clinicians, clinical trials patients and technology platforms to advance health discovery.

- Dedicated floors for Hudson researchers / laboratories
- Dedicated technology platforms floor
- Dedicated clinical trials floor
- Direct access to clinicians

Hudson Institute is ideally positioned to progress the rapid advancement of knowledge into life-changing and life-saving discoveries that drive solutions to our most pressing diseases.

Why Study at Hudson Institute?

Hudson Institute of Medical Research provides a collaborative, stimulating and nurturing environment for students to develop skills and confidence in basic and translational research. At Hudson, our research drives discoveries for Australia's most pressing health challenges and areas of global need.

173

Students,
Honours, Masters and PhD

56

Honours and PhD students graduated in 2015

56

Students published first-author research articles in 2015

Leading researchers and mentors

- Dedicated state-of-the-art technology platform floor
- Dedicated clinical trials floor
- Direct access to patients and clinicians through partnership with Monash Health

One-on-one student-to-supervisor contact

- Supportive teams – collaborative, approachable, friendly
- Opportunities to present your research nationally and internationally
- Dedicated research institution

Range of interesting and relevant projects

- Established and supportive student committees and social clubs
- Local, national and international networks
- Clinical and academic collaborations and partnerships

About Us

Hudson Institute of Medical Research is one of Australia's leading medical research institutes, specialising in driving innovative, cutting-edge research towards improved prevention, diagnosis and treatments.

Our 450 world-class scientists and postgraduate students are at the forefront of discovery science and translational research, bringing medical solutions to those who need it most. Our research is focused on our communities and Australia's most pressing health challenges and areas of global need. Our diverse research environment fosters sharing and collaboration, creating opportunities that spark unique insights and innovation.

The Institute is an NHMRC-accredited, not-for-profit, independent medical research institute, an affiliate of Monash University and Monash Health, and a partner in the Monash Health Translation Precinct (MHTP).

Hudson Institute is world-renowned for its research into women's and children's health, cancer, and infection and innate immunity, now closely tied to the latest new developments for cancer treatment.
We build upon a pioneering history of discovery that stretches back more than 50 years, from the development of current IVF technology, to changes in practices for the prevention of SIDS and the discovery of inhibin, which led to diagnostic tests for Down syndrome and certain ovarian cancers.

Our community is served by our clinical partner and Victoria's largest public health service, Monash Health. It is a rapidly growing, culturally diverse and ageing community.

Our breakthrough discoveries and ability to translate these into the clinic positively improve the lives of Australians at every life stage.

Our research is world-leading and responds to pressing health priorities.

Zoe Marks

Degree: MBBS/PhD, 3rd year

Area of Study: Type I IFN signatures in endocrine tumours

What do you hope to achieve as a researcher?

Completing a PhD at Hudson Institute has given me the opportunity to explore beyond clinical medicine. I am increasingly interested in oncology and aspire to continue work on breast cancer as a clinician-researcher.

Why did you choose Hudson Institute?

I stumbled upon the Hudson while chasing a specific project. Despite my initial ignorance, I now know this to be a unique medical research facility. Driven by youthful enthusiasm, Hudson Institute embraces researchers, clinicians and students alike, to tackle disease.

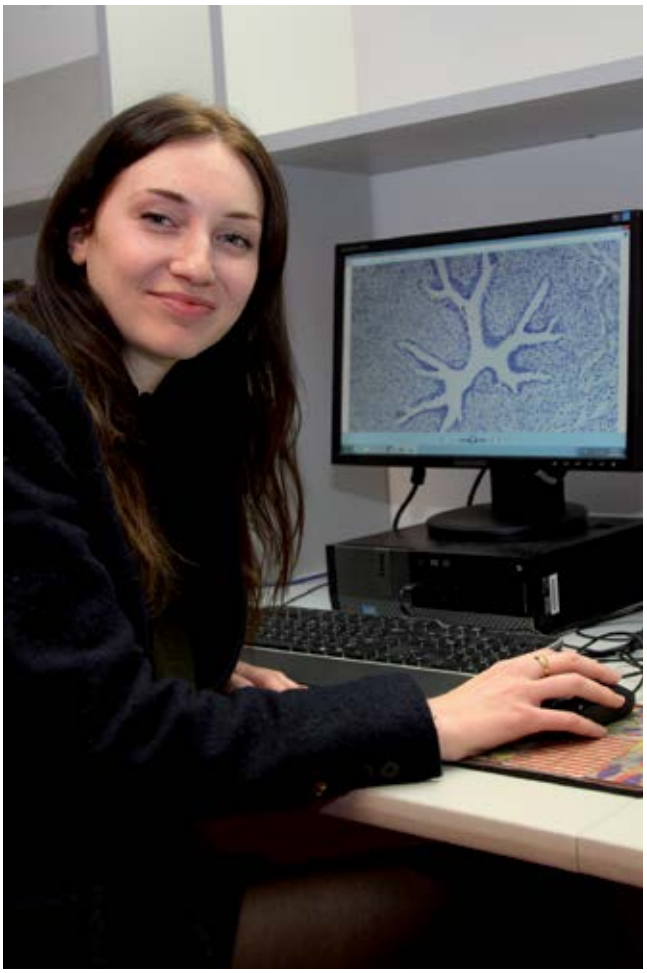
What is life like as a student at Hudson Institute?

It's pretty empowering to be a student here. Students are encouraged to take advantage of every opportunity and help to shape the 'Hudson', both academically and socially.

How has being a student at Hudson Institute helped you?

I'm a medical student with a clinical background and no previous research experience. Being at the Hudson has allowed me to take risks and plunge headfirst into the molecular basis of disease. Over the past three years, I've learnt to drive my own research and communicate it to the broader scientific community.

Stumble in or stride headlong — for a unique research experience come to the Hudson!



How has Hudson Institute helped your career options?

Being at the Hudson has ignited a life-long interest in medical research. I'm in awe of the power of successful research and the potential to impact whole populations; there are no limits to the depth to which you can go.

Mohamed Saad

Degree: PhD, 1st year

Area of Study: Investigating the regenerative effects of human amnion epithelial cells and their extracellular vesicles in lung and gut disorders

What do you hope to achieve as a researcher?

I want to become a great scientist! I wake up with excitement every morning with the prospect of learning something new and the chance to contribute to my research community, which will bring me a step closer to my dream.

Why did you choose Hudson Institute?

I chose to pursue my postgraduate studies at Hudson Institute because of its unique multidisciplinary research environment, which provides me with good career experiences and opportunities.

I am working and learning across stem cell research, cell biology, immunology, biochemistry and pathophysiology. That means I'm not confined to one area, but engaging with multiple disciplines.

What is life like as a student at Hudson Institute?

Hudson is a great environment with some world-leading researchers, so there is always someone interesting around to bounce ideas off.

What has being a student at Hudson Institute helped you achieve?

The facilities at Hudson are excellent, which means that my research is extensive, best-practice, and produced in the fastest possible time. My first research article will be submitted soon and that's been made possible by the supportive supervisors and colleagues.

What do you enjoy about your research?

The opportunity to learn so much is rewarding. I love making new discoveries and being able to contribute to the body of knowledge in my field, which will hopefully in time make a difference to clinical treatments.

What are the potential clinical benefits of your research?

I chose stem cell research because of its potential to treat incurable diseases. That makes it a compelling field.

Harriet Fitzgerald

Degree: PhD, 3rd year

Area of Study: How an altered uterine environment during the proliferative phase influences subsequent endometrial receptivity

Why did you choose Hudson Institute?

I have always been interested in reproduction and knew that I wanted to do research in female reproduction, and women's health in particular. When I was looking for an Honours project, the lab of Centre Head Lois Salamonsen was recommended to me.

I enjoyed my Honours research a great deal, as well as the strong student culture at Hudson Institute, and so I stayed on to do a PhD in the Endometrial remodelling lab.

What is life like as a student at Hudson Institute?

There are lots of opportunities to get involved in different events and activities as a student at the Hudson. I have been fortunate to be involved in the Hudson Institute Student Society (HISS) for the last three years as Assistant Treasurer, President and Secretary.

Each year HISS runs some fantastic events such as a Trivia Night, 3 Minute Thesis Competition, International Food Day, International Women's Day BBQ, Student Christmas Party and the annual Student Symposium.

These events create a cohesive, supportive and friendly environment for all students at Hudson Institute.

What has being a student at Hudson Institute helped you achieve?

Being a student at Hudson Institute has exposed me to life as a researcher at an independent medical research institute focused on translational research.

I don't think I would have had this same experience if I had conducted my project on campus at the university.

Conducting research at Hudson Institute helps to put medical research in context and helps you to understand how what we do in the lab can then be used in the clinic and hospital.

What do you enjoy about your research?

I enjoy the hands-on aspect and the fact that every day is different. It's exciting to be at the forefront of research into female reproduction and infertility.

Harriet Fitzgerald, President, Hudson Institute Student Society

What are the potential clinical benefits of your research?

My research aims to investigate whether a disturbance in the development of the lining of the uterus, the endometrium, during the proliferative phase of a woman's menstrual cycle may contribute to female infertility. By identifying changes in the development of the endometrium between fertile and infertile women, we may be able to develop novel treatments for infertility in women.

Describe a typical day in the lab.

A typical lab day involves planning and conducting experiments, checking on my cells, meeting with my supervisors, writing up results and protocols, attending student society meetings and chatting to my fellow peers.

Kim D'Costa

Degree: PhD, 3rd year

Area of Study: Effect of Helicobacter pylori interactions with host epithelial cells on inflammation and disease

Areas: Microbiology, innate immunology and infectious diseases

What do you hope to achieve as a researcher?

To enhance knowledge in the field of infectious diseases and hopefully provide a potential diagnostic or therapeutic option for patients.

Why did you choose Hudson Institute?

The research interests of CiiiD and Hudson Institute in general aligned with my personal scientific ambitions. The Hudson offered me a different work/research environment from what I had experienced as an undergraduate student.

What is life like as a student at Hudson Institute?

Being a part of a smaller group of like-minded individuals enables you to make friends easily and grow a supportive peer network.

There are numerous social opportunities for networking — not only other students, but also postdoctoral researchers and laboratory heads.

Being an active member of the Hudson Institute Student Society (HISS) has helped me to foster friendships while nurturing leadership, communication and organisational skills.

What has being a student at Hudson Institute helped you achieve?

It has helped me grow as a basic research scientist, while also exposing me to the importance of clinical and translational research. The proximity to the Monash Medical Centre and interaction with clinicians has also helped.

I have also enhanced my knowledge about different research areas by attending seminars, usually given by world-renowned speakers.

What do you enjoy about your research?

The opportunity to constantly learn new things with an aim to help society. It also sharpens my problem-solving skills and keeps me motivated.

There is also a strong focus on students presenting their research, which has significantly improved my ability to analyse and synthesise my data as well as communicate my research.

What are the potential clinical benefits of your research?

By contributing to the field of Helicobacter pylori, we can better understand how it persists in humans and what causes gastric carcinogenesis, to enable early detection of infection and more treatment options.

Describe a typical day in the lab.

Continuing a series of thought-out experiments to answer specific aims, analyse data generated, attend meetings/ seminars and most days have some spare time to catch up with colleagues for coffee/lunch.

Nadia Bellofiore

Degree: PhD

Area of Study: Female Reproductive Physiology

What do you hope to achieve as a researcher?

My goal is a seemingly simple one that most researchers share: to make a positive difference in the world, however big or small. I hope to achieve this through my work in reproduction and fertility to aid in treating women's reproductive disorders and diseases.

What is life like as a student at Hudson Institute?

You are always welcome at Hudson Institute. No one, supervisor or student, is shy. You are constantly surrounded by peers who excel in their field and it makes you strive to be the best. Your lab and Centre become one of the most nurturing and supportive groups throughout your studies.

What has been a student at Hudson Institute helped you achieve?

Hudson Institute is home to the only research colony of spiny mice in the Southern Hemisphere, and I have been one of the few lucky enough to work with these amazing little animals. Thanks to this rare opportunity, I discovered that the spiny mouse menstruates – something completely unheard of in rodents, which challenges almost everything we know about menstruating species.

What do you enjoy about your research?

I am particularly fond of working with the spiny mice. The most interesting part of my day is usually when I'm working either directly with the animals or learning something new about their tissues, organs and biology.

What are the potential clinical benefits of your research?

The discovery that the spiny mouse menstruates could potentially lead to huge advances in women's reproductive health, as until now, we haven't had a non-primate animal model to study menstruation. Disorders associated with menstruation affect hundreds of millions of women, and may even lead to common but poorly understood pregnancy conditions such as pre-eclampsia. My work uses the spiny mouse as a model for human menstruation, and we are looking to see if they might show some of the diseases of women. If they do, we could be on the way to revolutionizing the way women's reproductive health is studied.

Ishmael Inocencio

Degree: PhD, 1st year Bachelor of Biomedical Science

Area of Study: Reducing morbidity and mortality of fetal growth restricted infants

What do you hope to achieve as a researcher?
To provide information that will one day help improve the lives of infants that have been given an unlucky start to life.

Why did you choose Hudson Institute?
I wanted a place that was still part of 'Monash', but I didn't want to feel like I was simply back at uni.

What is life like as a student at Hudson Institute?
Great. You are given the freedom to discover things on your own, but are never left unsupported.

What has being a student at Hudson Institute helped you achieve?
I've now been to a few conferences, local and interstate, and been able to show others the great work we do.

What do you enjoy about your research?
The camaraderie you develop with the team and sense of accomplishment when you all work together and get good results.

What are the potential clinical benefits of your research?
Improving cardiovascular morbidity and mortality in fetal growth restricted infants.

Describe a typical day in the lab.
Science, science and more science.

Paulo Pinares-Garcia

Degree: PhD, 3rd year

Area of Study: The role of the Y-chromosome gene SRY in male Parkinson's disease

What do you hope to achieve as a researcher?
I've been able to achieve a true appreciation for the role that medical research plays in our community. We're here to make discoveries that could one day lead to a discovery or cure, and that has given me a tremendous amount of self-belief for the work that I'm doing.

Why did you choose Hudson Institute?
I chose the Hudson Institute in 2013 as an Honours student, due to a chance encounter with a childhood friend who worked as a Research Assistant in my supervisor's lab. She got me hooked with the type of novel research they were doing. You could really say that I didn't choose the Hudson, the Hudson chose me!

What is life like as a student at Hudson Institute?
Being based off-campus, student life feels like a community of like-minded students. We're all there to support each other. Being on the Hudson Institute Student Society (HISS) Committee has given me the opportunity to have a greater say in the role of students. From this I've made solid friendships that I hope will be life-long.

What do you enjoy about your research?
I enjoy the broad spectrum of work that I can get involved in. No two days are the same, and the novel aspect of my work makes each discovery worthwhile. One day it might be working with animal models, the next sectioning or an RT-PCR-reverse transcription polymerase chain reaction experiment.

What are the potential clinical benefits of your research?
SRY inhibition in the male brain may be a novel therapeutic target that prevents the progression of Parkinson's disease in males, who are two times more susceptible to the disease than women.

Describe a typical day in the lab.
No day in the lab is quite the same — and that's the great thing about it. More than likely I'm performing a behaviour test, or starting an overnight experiment.

COURSES AVAILABLE

WHAT TO DO:

1. Choose an area(s) of research that interests you.

2. Read about the projects in this handbook and visit the Hudson Institute website www.hudson.org.au to identify the Research Centre(s), Group Head(s) and their teams.

3. Call or email the project contact to arrange a time to discuss the research and meet the team. You can do this at any time throughout the year.

Make the most of our Student Open Day, held in August. Meet the supervisors and teams, and explore the laboratories, platform technology facilities and clinical trials floor.

Honours Programs:

- Bachelor of Science (Honours) – including Bachelor of Biotechnology (Honours)
- Bachelor of Medical Science (Honours)
- Bachelor of Behavioural Neuroscience (Honours)

For further information, contact:

Associate Professor Mark Hedger
Honours Coordinator
Email: mark.hedger@hudson.org.au

Ms Roseline Acker
Administration Officer (Honours program)
Email: roseline.acker@hudson.org.au

Bachelor of Biomedical Science (Honours):

Dr Tony White
Bachelor of Biomedical Science (Honours) Co-ordinator
Email: tony.white@monash.edu

Postgraduate Research Programs:

- Doctor of Philosophy
- Doctor of Medicine
- Research Masters

For further information contact:

Professor Kate Loveland
Head of Postgraduate Studies,
School of Clinical Sciences & Hudson Institute
Email: phd.scs@monash.edu

Ms Rachael Unwin
Postgraduate Administration Officer
Email: rachael.unwin@monash.edu

HOW TO APPLY

NON-MONASH UNIVERSITY STUDENTS

While Hudson Institute students predominantly come from Monash University, we also welcome applications from other Australian Universities and overseas. In addition to the information in the following pages, you will need to provide details of courses you have studied and a certified transcript of your academic record so that we can give you appropriate credit.

HONOURS

The Honours courses aim to provide students with a higher level of experience in independent analysis and research in their chosen area of expertise.

Each Honours course has its own requirements and deadlines. Therefore, it is advisable to check the relevant Faculty and department websites, and begin looking for potential research projects/supervisors early in second semester.

Bachelor of Science (Honours)

You must meet the requirements of the department in which you intend to undertake the coursework component of the course. This is usually a distinction grade average (70%) or above, in 24 points of studies in relevant units at level three. The coursework component of your Honours year will be run by the department in which you enrol. This will be the one most appropriate to your research component, and need not necessarily be the one in which you undertook your level three major studies. Your research component can be carried out at the Hudson Institute (MMC4100).

The Honours application form can be downloaded from:
http://www.monash.edu/science/future-students

Bachelor of Biomedical Science (Honours)

You must meet the requirements of the department in which you have majored; for students this is usually a distinction grade average (70%) across BMS3021 and BMS3042, and 12-24 points of studies at level three units. Acceptance of external applicants is based on an individual assessment of their academic record in relevant areas of study.

The Biomedical Research Project component of your Honours year (BMS4100) is run by the School of Clinical Sciences (SCS) / Hudson Institute, based at the Monash Medical Centre, and the coursework component of your Honours year (BMS4200) is run jointly by SCS / Hudson Institute and the School of Biomedical Sciences.

The BMS Honours application form can be accessed from:
http://www.med.monash.edu.au/biomed/honours

Apply online at E-Admissions:
http://applicant.connect.monash.edu/connect/webconnect

Bachelor of Medical Science (Honours)

This one-year research program is available to students who have successfully completed at least two years of medical studies by the end of 2016. There is the opportunity to convert the BMedSc to a PhD. This new initiative of MBBS/PhD allows students to accelerate their research studies and complete a PhD in 2.5 rather than 3.5 years. Eligible students require a mark of H1 for their BMedSc project and can apply for a scholarship to complete their PhD. The degree of BMedSc is not taken and the research carried out in that year is incorporated into the PhD. Students intermit from Medicine whilst doing this.

Students wishing to take this opportunity should discuss the possibility with their supervisor early in their BMedSc year and also with the Head of Postgraduate Studies: Kate.Loveland@monash.edu

Students who are undertaking a medicine program at a university other than Monash must have completed equivalent studies corresponding to a minimum of two years of the Monash University undergraduate MBBS program.

There is now the option of completing a BMedSc after graduation with an Australian or New Zealand MBBS.

Information regarding the program is available online:
http://www.med.monash.edu.au/bmedsci/

Bachelor of Behavioural Neuroscience (Honours)

The Honours year in Behavioural Neuroscience aims to extend research training in specialised areas of behavioural neuroscience, and to help students acquire sophisticated research skills. It is a course requirement that the research project component of the Honours year has significant 'Behavioural Neuroscience content' (students must gain course coordinator's approval prior to the initiation of the research project).

Honours in the Bachelor of Behavioural Neuroscience is offered to students who have completed the undergraduate BBNSc degree with 70% average or better in 24 credit points of core third year behavioural neuroscience subjects, as well as meeting entry requirements for their chosen program. Information regarding the program is available online:
http://www.med.monash.edu.au/psych

Doctor of Philosophy (PhD) / Master of Biomedical Science

Students wishing to complete advanced research training should enrol for either a Research Masters or PhD degree. The prerequisite for enrolment in these programs is an Honours degree HIIA or above, or equivalent.

Introduced in 2015, the new Monash Doctoral Program includes a coursework or professional development component, setting the Monash PhD apart from all other Australian PhDs. There are seven different programs available across the Faculty of Medicine, Nursing and Health Sciences, and students can tailor their program to suit their individual needs.

The duration of full-time PhD candidature is 2–4 years. Typically, a PhD candidate holds a scholarship, which provides support for a maximum of 3.5 years. Thesis assessment is made by examiners external to the department in which you are studying, selected because of their expertise in the candidate's field of research.

Applications for PhD and Masters can be made any time throughout the year. It is essential to have obtained a supervisor before commencing the application process. Scholarship applications generally close on 31 October and 31 May each year, so make sure you check the Monash University website well in advance for these details.

Application forms are available through the Monash University website:
http://www.monash.edu.au/migr/apply/

There may be departmental scholarships available. Contact individual supervisors for details of these. Information regarding scholarships is available through the Monash University website:
www.monash.edu.au/scholarships/








POSTGRADUATE STUDENT COMMITTEE

The Committee aims to ensure that each student is able to manage their workload, expectations, career development and any conflict issues that may arise. The Committee coordinates higher degree confirmations, mid-candidature reviews, pre-submission seminars and PhD scholarship applications. It also runs instructional sessions on time management, thesis writing and scholarship applications. Students are monitored annually and have the opportunity to present at the annual SCS / Hudson Institute Student Symposium.

STUDENT SUPPORT PROGRAMS

HUDSON STUDENT VACATION PLACEMENT PROGRAM

The Hudson Student Vacation Placement Program is a scheme designed to give undergraduate and Honours students experience in an area of research and an insight into future career opportunities, supplemented by a scholarship payment for the placement period. Placements are tenable for 6–8 weeks; the exact length is to be negotiated between the student and their nominated supervisor. Applicants are required to nominate one of the three available intake start dates between November and January. The placements are not intended to support the employment of students for routine work.

Eligibility

The scheme is open to University undergraduates who have completed at least two years of their course at the time the placement commences. Undergraduates who have completed their final year and students currently finishing an Honours year will be eligible only if they can demonstrate plans to undertake further study the following year. Before applying, the student should contact a supervisor and receive written acceptance to join their laboratory.

Application Process

Choose an intake date and apply by the closing date.

For the 2016–2017 summer vacation periods, placements are offered to commence on one of three set dates. Applications must be received by the closing date of the chosen intake. Late applications will not be considered.

How to Apply:

Applicants will need to contact their proposed project supervisor, and then complete the online application form by the closing date below, matching the corresponding start date.

	Start Date	Closing Date
1	7 November 2016	5 pm Friday 28 October 2016
2	28 November 2016	5 pm Friday 28 October 2016
3	9 January 2017	5 pm Monday 14 November 2016

For further information please visit:
http://hudson.org.au/students/student-vacation-placement-program-2015-2016/

or contact **Dr Mai Sarraj** from our Grants Team at:
grants@hudson.org.au

HUDSON INSTITUTE STUDENT SOCIETY

The Hudson Institute and School of Clinical Sciences Student Society is a student-run society that organises social events, and facilitates student education and training. The student society represents the interests of all students within the Institute and welcomes students from Monash University's School of Clinical Sciences to also become members of the society. The Student Society aims to create a positive social and academic environment, enabling all students to excel in their research degrees.

Committee Members

President: Kimberley D'Costa
Vice President: Paulo Pinares-Garcia
Treasurer: Zoe Marks
Secretary: Harriet Fitzgerald
Event and Creative Officer: Ishmael(Mikee) Inocencio
Early Career Researcher Representatives: Katharine Johnson and Catherine Cochrane

Centre Representatives

Centre for Reproductive Health (CRH) and Centre for Endocrinology and Metabolism (CEM):
Hannah Loke, Aleisha Symon, Brittany Croft

Centre for Cancer Research (CCR):
Dean Popovski, Francesca Raffaelli

Centre for Genetic Diseases (CGD):
Abena Nsiah-Sefaa

Centre for Innate Immunity and Infectious Diseases (CiiiD):
James Ong, Michelle Chonwerawong, Madelynne White

The Ritchie Centre (TRC):
Krishan Singh, Aiden Kashyap

School of Clinical Sciences (SCS):
Kathryn Pramekumar

CENTRE FOR CANCER RESEARCH

Centre Head: Associate Professor Ron Firestein

Scientists working in the Centre 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.

Key areas of interest:

- 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 steroid hormones and nuclear receptors in breast cancer development and progression
- Role of peptidase activity on inflammatory signalling and tumour microenvironment in ovarian cancer.

Research Groups and Heads:

Cancer Genetics and Functional Genomics: A/Prof Ron Firestein

Cancer and Innate Immunity: Prof Bryan Williams, Dr Tony Sadler

Oncogenic Signalling: Prof Terrance Johns

Cancer Drug Discovery: A/Prof Colin Clyne

Developmental and Cancer Biology: Dr Jason Cain

STAT Cancer Biology: Dr Daniel Gough

Ovarian Cancer Biomarkers: Dr Andrew Stephens

Metabolism and Cancer: Dr Kristy Brown

Immunohaematology: Dr Ashish Banerjee, Dr George Grigoriadis (Monash Health)

Genetics and Molecular Pathology: A/Prof Elizabeth Algar (Monash Health),

Prostate Cancer Biomarkers: Dr Arun Azad (Monash University, School of Clinical Sciences)

Leukaemia and Myelodysplasia: A/Prof Jake Shortt (Monash University, School of Clinical Sciences)

RESEARCH GROUP: Cancer Genetics and Functional Genomics

1. Functional genomic screens to identify new therapeutic targets for bowel cancer

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Ron Firestein

Email: ron.firestein@hudson.org.au

Phone: 03 8572 2774

Project Description: Bowel/colon cancer is a major cause of cancer-related morbidity worldwide. We will use novel genomic technologies (e.g. CRISPR, shRNAs) to screen the cancer genome in an effort to identify novel therapeutic targets for colon cancer patients.
Keywords: genetics, genomics, cancer, screen, personalised medicine

2. How can we do a better job detecting cancer in patients? Devising new strategies and technologies using blood-based biomarkers

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Ron Firestein

Email: ron.firestein@hudson.org.au

Phone: 03 8572 2774

Project Description: Early detection of cancer is a key determinant of patient survival. This project utilises a new class of biomarkers called non-coding RNA (ncRNA) that are differentially expressed in cancer compared to normal tissues. In this project, we will determine the value of non-coding RNA in predicting cancer and patient response to cancer therapies.
Keywords: genetics, genomics, cancer, diagnostics, non-coding RNA, personalised medicine

3. Transcriptional regulators as cancer targets: new models and therapeutic approaches

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Ron Firestein

Email: ron.firestein@hudson.org.au

Phone: 03 8572 2774

Project Description: Transcriptional regulators play a key role in activating oncogenic pathways that impinge on tumour growth, invasion and metastasis. We have recently used CRISPR to generate cancer cell lines with fluorescent and luminescent reporters of key transcriptional pathways in colorectal cancer. In this project, the student will utilise cell biology and molecular biology techniques to dissect the components of the transcriptional machinery in cancer and identify new therapeutic targets.
Keywords: genetics, genomics, cancer, oncogenes, transcription

4. Understanding cancer resistance to chemotherapy

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Ron Firestein

Email: ron.firestein@hudson.org.au

Phone: 03 8572 2774

Project Description: The majority of cancers initially respond very well to standard-of-care chemotherapeutics, but invariably become resistant, leading to cancer relapse and patient mortality. This project seeks to identify novel therapeutic targets that will re-sensitise tumours to chemotherapies in the resistant setting.
Keywords: chemotherapy, cancer treatment, drug targets, screen, genetics

5. Development of new 3-dimensional models of cancer to model drug resistance and develop new cancer treatments

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Ron Firestein

Email: ron.firestein@hudson.org.au

Phone: 03 8572 2774

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 as 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.
Keywords: colon cancer, organoids, models

RESEARCH GROUP: Cancer and Innate Immunity

6. Kinase capture

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Anthony Sadler

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Phone: 03 8572 2772

Project Description: We have established a protocol to capture transient protein-protein interactions that we wish to use as a novel discovery tool to identify specific kinases that phosphorylate a particular protein substrate. This approach aims to inform subsequent strategies to pharmacologically target cell-signalling processes that modulate disease. The project will establish and validate an expression library of the human kinome, before endeavouring to identify kinases of orphan protein substrates.
Keywords: protein kinase, protein interaction, cell signalling

7. Role of PKR in obesity

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Anthony Sadler

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Project Description: Obesity-related conditions, predominantly fatty-liver, cardiovascular disease and diabetes, constitute significant health issues in the western world. Therefore there is a necessity to decipher pathological processes caused by obesity in order to develop strategies to amelioration the resulting burden to healthcare. Towards this, we have identified a role for the immune protein kinase R (PKR) in modulating obesity-related conditions in a murine model of diet-induced obesity. A project exists to investigate the relative contribution of the different PKR-dependent effectors of metabolic disease that have been identified to date.
Keywords: obesity, metabolism, metabolic pathways

8. Development of broad-spectrum antivirals

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Anthony Sadler

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Project Description: We have described a role for protein kinase R in maintaining cell homeostasis via an interaction with the actin remodelling protein, gelsolin (Irving A et al Immunity 2012). This interaction provides broad-spectrum antiviral protection against viruses that employ actin remodelling as part of their infection process. These observations have opened up possibilities of screening for compounds that modulate actin remodelling. A project exists to establish assays to identify compounds that modify actin remodelling and to assess their antiviral activity. This approach will provide new information on virus-cell interactions, and potentially lead to the identification of novel targets and a development pipeline for broad-spectrum antivirals.
Keywords: cell cytoskeleton, virus entry, infection, actin modifiers

9. Regulation of inflammation in cancer

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Dakang Xu

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Project Description: The role of Toll-like receptors (TLRs) and innate immune responses in inflammation-associated carcinogenesis is under active investigation. TLR signalling can both promote and eliminate developing tumours, and sculpt tumour immunogenicity. It is becoming increasingly apparent that inflammation plays an important role in the progression of cancer, from the results of TLR-related animal studies. According to our data, transcription factors PLZF and ATF3 negatively regulate cytokine production. We propose to examine how these transcription factors contribute to anti-tumour responses through negative regulation of TLR signalling in inflammation-induced cancer and during primary tumourigenesis. We will use mouse models of bladder and colon cancer, and confirm our results in human cancers.
Keywords: inflammation, inflammasome, microbiota, tumourigenesis

10. Epigenetic control of inflammatory disease

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Dakang Xu

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Phone: 03 8572 2721

Project Description: Epigenetic control mechanisms during the inflammatory response play a fundamental role in gene expression. Molecules have been developed that interact with epigenetic marks on DNA. We have found that such molecules have strong anti-inflammatory effects in macrophages. In this project, we will investigate the epigenetic marks in macrophages, as well as inflammatory cells in inflamed tissues in conditions such as sepsis, rheumatoid arthritis, inflammatory bowel disease and other chronic inflammatory diseases. We also propose to characterise genetically modified mouse models of inflammation, as well as investigate preclinical models and clinical trial material.
Keywords: epigenetics, reprogramming innate immunity, novel therapies

11. Role of the inflammatory microenvironment in development of colon cancer

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Prof Bryan Williams

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Phone: 03 8572 2705

Project Description: We are examining the role of pro-inflammatory signalling in colon cancer progression using a mouse model of colitis-associated cancer. By selective deletion of the integrin-linked kinase (ILK) gene in myeloid cells we observe a significant reduction in colonic inflammation, as evidenced by reduced macrophage infiltration and improved disease index. Importantly, reduced colonic inflammation in the ilk knockout mice significantly reduces tumour incidence, indicating that pro-inflammatory ILK signalling in the monocytic compartment promotes tumourigenesis. A key event in pro-inflammatory ILK signalling is activation of the nuclear transcription factor, NF-κB, which regulates production of pro-inflammatory cytokines such as TNF-κ. We are studying unique regulation of intracellular NF-κB signalling by ILK, as well as profiling cytokine and cancer-related protein signatures in colon tumours and in tumour-associated macrophages (+/- ILK), in order to understand the role of ILK in pro-tumourigenic regulation by the innate immune system. Accordingly, we are developing and testing small molecule ILK inhibitors in vivo as potential therapeutics to block pro-inflammatory signalling within the tumour microenvironment, and thereby suppress tumour growth.
Keywords: colon cancer, integrin-linked kinase (ILK), inflammation, nuclear factor κB (NF-κB), mouse models

RESEARCH GROUP: Oncogenic Signalling

12. Understanding and overcoming resistance to EGFR therapeutics in high-grade glioma

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Prof Terrance Johns

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Phone: 03 8572 2708

Project Description: High-grade glioma (HGG) is the most common and aggressive type of malignant primary brain tumour and is among the most lethal cancers. Despite modern advances in therapeutic intervention, HGG remains incurable. A hallmark of HGG is the activation (by either gene amplification or mutation) of the epidermal growth factor receptor (EGFR), making it a prime target for therapy. Although EGFR is aberrant in 57% of HGGs, attempts to therapeutically target EGFR in HGG patients with antibodies or small molecule inhibitors have failed so far. We therefore need to gain a better understanding of patient responses to EGFR inhibitors in the clinic.

To do this, we will assess the EGFR status and associated signalling of various cell lines derived from HGG patient tumours, in order to determine which tumours are most likely to respond to treatment with EGFR inhibitors. In addition, we will investigate other mechanisms that may be causing resistance to EGFR inhibitors and determine whether these alternate pathways can be co-targeted to augment anti-EGFR therapy.
Keywords: brain cancer, EGFR, targeted therapies

RESEARCH GROUP: Cancer Drug Discovery

13. Nuclear receptor pharmacology

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Colin Clyne

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Phone: 03 8572 2504

Project Description: Anti-oestrogen therapies, while very successful in the treatment of many breast cancers, are not effective for patients whose tumours do not express the oestrogen receptor. Many patients who do respond to these drugs eventually become resistant to their effects. We are identifying alternative molecules related to the oestrogen receptor (nuclear receptors) that could be exploited as novel breast cancer therapeutics.
We have shown that one such receptor, LRH-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 LRH-1 interacts strongly with the oestrogen biosynthetic pathway. To verify our findings and aid understanding of the role of LRH-1 in both the normal breast and breast cancer, we have developed a transgenic mouse model in which expression of human LRH-1 is directed specifically to the mammary gland. We have also shown that LRH-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 these animal model and in vitro pharmacology approaches.
Keywords: breast cancer, nuclear receptors, oestrogen, co-regulators

14. Understanding resistance to breast cancer therapies

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Colin Clyne

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Project Description: Most breast cancer patients have tumours that require the female sex hormone oestrogen to grow and develop. Blocking this action of oestrogen (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.
Keywords: breast cancer, oestrogen, therapeutic resistance, co-regulators

RESEARCH GROUP: Developmental and Cancer Biology

15. Investigating a role for the Hedgehog signalling pathway in bone development and disease

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Jason Cain

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Phone: 03 8572 2720

Project Description: Hedgehog (Hh) signalling is a critical embryonic signalling pathway that governs normal bone development. We have recently uncovered that aberrant Hh pathway activity is directly implicated in the pathogenesis of osteosarcoma, the most prevalent primary tumour of bone and second-leading cause of cancer-related death in children and young adults. Using a series of unique genetic mouse models, the successful candidate will investigate: (1) the role of the Hh signalling pathway in normal and abnormal bone development; and (2) determine the effects of aberrant Hh signalling on the initiation of osteosarcoma.
Keywords: Hedgehog, osteosarcoma, bone development

16. Interrogation of MYC functions in neural development and cancer

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Jason Cain

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Project Description: Medulloblastoma is a highly malignant tumour of the cerebellum and the most prevalent paediatric brain tumour, accounting for ~20% of all primary childhood CNS cancers. Amplification or overexpression of the MYC family of proteins is a feature of many cancers, including medulloblastoma. Utilising novel genetic mouse models, this project will interrogate the functions of MYC overexpression in the neural lineage during development and in the initiation of CNS tumours.
Keywords: MYC, neural development, mouse models

RESEARCH GROUP: Ovarian Cancer Biomarkers

17. Targeting DPP4 as a novel therapeutic strategy for ovarian cancer management

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Andrew Stephens

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Project Description: Dipeptidyl peptidase 4 (DPP4) is an enzyme that regulates the bioactivity of many small peptides and proteins involved in cell metabolism, growth, signalling and

innate immunity. We recently discovered that DPP4 promotes the pathogenesis of ovarian cancers by suppressing the immune response. DPP4 is an attractive therapeutic target for treatments aimed at promoting anti-tumour immunity, an area of intense research interest for many tumour types. The DPP4 inhibitor sitagliptin is prescribed for the management of type II diabetes, and we hypothesise that it may be repurposed for the treatment of ovarian cancer. This project will evaluate how DPP4 contributes to the biology and pathogenesis of ovarian cancers, both in vitro and in vivo; and whether sitagliptin treatment, in combination with (i) standard chemotherapy and/or (ii) experimental cell cycle checkpoint inhibitors, can be repurposed as a novel therapeutic approach for cancer treatment.
Keywords: dipeptidyl peptidase, ovarian cancer, sitagliptin, chemokine, CXCL10

18. Role of DPP4 in spheroid-mediated ovarian cancer metastasis

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Andrew Stephens

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Project Description: The growth and spread of tumour cells is a major problem in ovarian cancer management, where most patients are initially diagnosed with extensively disseminated disease. Metastases arise through the passive spread of spheroids, which are small, heterogeneous aggregates of tumour cells that acquire stem cell-like properties and are resistant to chemotherapy. Spheroids are released from the surface of growing ovarian tumours to infect other organs within the peritoneal cavity. New therapies to block tumour spread would significantly improve the treatment options for ovarian cancer patients. We recently identified that the enzyme dipeptidyl peptidase 4 (DPP4) is involved in the pathogenesis of ovarian cancer, and that its expression is regulated by low oxygen conditions, similar to those present in the tumour microenvironment. Spheroids exist around a hypoxic core; thus, DPP4 expression may be an important feature for their formation, structural integrity and survival. This project will investigate the expression, localisation and function of DPP4 in spheroids in vitro, and its roles in maintaining spheroid structure and promoting invasiveness.
Keywords: dipeptidyl peptidase, ovarian cancer, metastasis, hypoxia, spheroids

19. Therapeutic antibodies to block ovarian cancer spread

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Andrew Stephens

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Project Description: Unlike other tumour types, ovarian cancers spread rapidly by shedding tumour cells from their surface, which then implant at other sites in the peritoneal cavity. In the period between attachment at new sites and invasion into the underlying tissue, tumour cells undergo transcriptional reprogramming to switch from a proliferative to an invasive phenotype. Therapies directed at cells during this reprogramming phase would be highly advantageous for the prevention of further metastasis, to stabilise or assist in clearing existing disease. We have identified several proteins transiently expressed by tumour cells during the reprogramming phase that are required for invasion into underlying stromal layers. Excitingly, antibodies targeting some of these can block invasion in vitro – suggesting their suitability as therapeutic targets. This project will characterise the functional roles of some of these proteins in tumours both in vitro and in vivo; and will commence the identification of surface-exposed epitopes for the generation of therapeutic antibodies.
Keywords: ovarian cancer, invasion, metastasis, chemoresistance

20. Understanding tumour progression: how does anti-tumour immunity sculpt the transcriptional landscape of ovarian cancer?

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Andrew Stephens

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Project Description: High-grade serous ovarian cancers (HGSOCs) are the most common type of ovarian tumour, and appear to arise primarily from the secretory epithelium in the fallopian tube. Unlike other ovarian cancers, HGSOCs have no clear mutational pathway and appear to be largely driven by copy number changes. Molecular analyses have identified five subtypes of these tumours, based on their expression patterns; however, HGSOCs are highly heterogeneous and generally contain multiple molecular subtypes. Our current knowledge of immune editing suggests that anti-tumour immunity is a crucial factor in this process, influencing and directing tumour phenotype according to stage of progression and localisation of disease. This project will examine how selective pressure imposed by the anti-tumour immune response contributes to stage-specific pathogenesis and immune sculpting of ovarian tumours over time; and the contribution of tumour suppressor p53, a ubiquitous driver mutation in the development of high-grade serous epithelial ovarian cancers, to the alteration of tumour transcriptional patterns in vitro and in vivo during tumour progression.
Keywords: immunoediting, lymphocyte, ovarian cancer, metastasis, chemoresistance, p53

21. Validation of a novel theranostic assay for ovarian cancer

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Andrew Stephens

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Phone: 03 8572 2686

Project Description: CXCL10 is a chemokine that controls the recruitment of T-cells in vivo, and is an important part of the early immune response. In ovarian cancers, we have found that CXCL10 can be modified to an inactivating form that actually prevents

a correct immune response from occurring, thus promoting tumour progression. We have developed a novel assay to measure inactivating CXCL10 in ovarian cancer patients, to assist in informing ovarian cancer diagnosis, prognosis or therapies. This project will explore the use of 'inactivating' CXCL10 measurement to monitor tumour progression and response to therapy in a preclinical mouse model, and will support ongoing clinical trials validating CXCL10 measurement and therapeutic targeting in ovarian cancer patients.
Keywords: T-cell, lymphocyte, cancer, chemokine, dipeptidyl peptidase, diagnostic

22. Exploring chemokine inactivation in the ovarian tumour microenvironment

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Andrew Stephens

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Phone: 03 8572 2686

Project Description: CXCL10 is an important chemokine that controls the early recruitment of T-cells to combat wounding and/or disease. We recently discovered that some ovarian cancers contain a modified form of CXCL10 that can directly suppress T-cell migration, thus preventing a productive anti-tumour immune response from occurring. The frequency and effects of this modification in ovarian cancers have never been explored. This project will analyse the in vitro and in vivo effects of modified CXCL10, including its unknown potential effects on apoptosis, paracrine signalling and transcriptional activity in cells, and its direct effects on the tumour microenvironment.
Keywords: chemokine, dipeptidyl peptidase, T-cell, migration, microenvironment

RESEARCH GROUP: Metabolism and Cancer

23. AMPK, new subunit-specific roles in cancer growth and metastasis

Theme: Cancer

Suitability: Honours

Project Leader: Dr Kristy Brown

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Phone: 03 8572 2520

Project Description: We have previously shown that AMPK is a negative regulator of oestrogen production in the breast. AMPK is a heterotrimeric enzyme composed of three subunits: α, β and γ. We have found that β subunits are altered in cancer and appear to be drivers of cancer metastasis. This project will explore the role and regulation of AMPK β subunits in breast cancer growth and metastasis using CRISPR gene silencing and xCelligence cell proliferation, migration and invasion assays.
Keywords: breast cancer, metastasis, AMPK

24. Fat and breast cancer-derived exosomes as drivers of oestrogen production

Theme: Cancer

Suitability: Honours

Project Leader: Dr Kristy Brown

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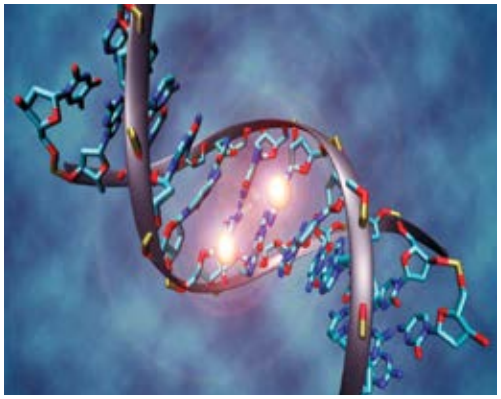
Phone: 03 8572 2520

Project Description: Most breast cancers are oestrogen dependent. Despite a decrease in breast cancer-related deaths, high obesity rates have contributed to a steady rise in incidence in older women. Obesity is associated with dramatic changes in adipocyte biology. Recently, interest has also turned to the gut microbiota, which is different in lean and obese individuals. Exosomes are membrane-covered vesicles secreted by many cell types, including tumour cells and adipocytes, that can interact with target cells. These structures carry proteins and genetic material, which have the potential to impact gene expression in target cells. Bacteria also produce exosome-like membrane vesicles (MVs). MVs are found in blood and are believed to have effects on host cells. My research team has made major advances in understanding how aromatase, responsible for converting androgens into oestrogens, is regulated in breast fat. However, there have been no reports examining the effect of exosomes on aromatase in any tissue. In our pilot studies, we have made the discovery that exosomes from fat, breast cancer cells and bacterial MVs can stimulate the expression of aromatase in breast adipose stromal cells (ASCs). We hypothesise that exosomes produced in obesity and breast cancer are key drivers of aromatase expression in the breast adipose tissue. Our aims are to:
1) characterise obesity- and breast cancer-associated exosomes isolated from human serum, adipose tissue and isolated breast cancer cells, adipocytes and obesity-associated bacteria;
2) demonstrate that obesity- and tumour-associated exosomes stimulate aromatase expression in breast adipose stromal cells;
3) identify the cargo of exosomes responsible for stimulating aromatase expression.
Keywords: breast cancer, aromatase, oestrogen, exosome, obesity



RESEARCH GROUP: Immunohaematology

25. Role of NF-κB in haematological malignancies

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Ashish Banerjee

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Project Description: The alternate NF-κB pathway is increasingly being recognised as an important player in chemoresistance in haematological malignancies like multiple myeloma, chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL). The NF-κB inducing kinase (NIK) is the driver of this pathway, which promotes cancer cell proliferation and survival. This project will use state-of-the-art techniques, including CRISPR and shRNA-mediated knockdown, ChIP sequencing and mouse models to understand the mechanism of NIK-dependent growth of malignant cells.
Keywords: lymphoma, multiple myeloma, gene editing

26. The crosstalk between NF-κB and Stat3 in B cell homeostasis and function

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Ashish Banerjee

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Phone: 03 8572 2719

Project Description: Gain of function mutations in Stat3 have been associated with aberrant lymphoproliferation and lymphoid cancers in humans. We have found that mice lacking an NF-κB family transcription factor, NF-κB1, exhibit aberrant lymphoproliferation, which coincides with increased levels of activated Stat3. Although crosstalk between NF-κB and Stat3 signalling pathways has been reported in several cancers, the mechanism of this interaction remains unclear. This project will delineate the precise role of NF-κB1 in suppressing Stat3 signalling, using mouse genetics, shRNA knockdown and cell culture techniques.
Keywords: B-cell lymphoma, NF-κB, Stat3

27. Iron chelation therapy to overcome chemoresistance in haematological malignancies

Theme: Cancer

Suitability: Honours, PhD

Project Leader: Dr Ashish Banerjee

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Project Description: Resistance to chemotherapy is a major hurdle in the treatment of many different cancers, including haematological malignancies. Iron is an essential element that is indispensable for diverse cellular processes. Cancer cells alter their iron metabolism pathways, which they use for enhanced growth and proliferation. Therefore, iron chelation can be used as a novel therapeutic approach to overcome chemoresistance in the treatment of cancer. Using cutting-edge techniques, this project will systematically address the impact of iron chelation in leukaemia cell lines and primary human leukaemia in vitro and in mouse models.
Keywords: chemotherapy, iron chelation, leukaemia

RESEARCH GROUP: Genetics and Molecular Pathology

28. Functional analysis of genomic imprinting in childhood cancer

Theme: Cancer

Suitability: Honours, PhD

Project Leader: A/Prof Elizabeth Algar

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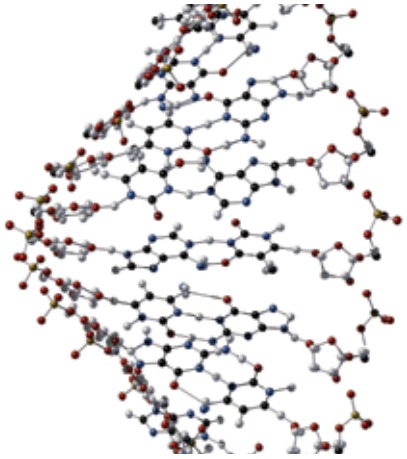
Project Description: Genomic imprinting is a process through which it is possible to control gene dosage from the parental chromosomes in early development, by epigenetic modification of locus control regions (lcrs). Several genes imprinted are important in childhood cancer, with accumulating evidence that disruption to the imprinting process is a critical step in the initiation of certain childhood cancers. This project concerns the identification of genetic factors that control and disrupt the imprinting process through the interrogation of the genomic landscape in the paediatric kidney cancer, Wilms tumour. The project is a translational research project in which students will learn to use state-of-the-art genetic techniques to address this question.
Keywords: childhood cancer, genomic imprinting



CENTRE FOR ENDOCRINOLOGY AND METABOLISM

Centre Head: Professor Peter Fuller AM

The complex endocrine system impacts all aspects of health and disease. As the pre-eminent Australian centre for endocrinology research, our laboratories undertake basic and clinical research.

Our goal is to improve understanding of the role of hormones in human biology and disease in order to tackle key health challenges facing Australian and global communities, including reproductive health, bone health, cardiovascular disease, endocrine cancer and obesity. Clinical translation of these findings to improve diagnosis, therapeutic interventions and prevention of disease remains a key focus for the group.

Key areas of interest:

- The management and treatment of metabolic bone disease, particularly osteoporosis, in under-served patient groups.
- Cardiovascular disease and the mineralocorticoid receptor (MR), primarily how the MR controls fibrosis and inflammation in the heart muscle and immune cells (macrophages).
- The role of reproductive hormones in regulating processes within the body, particularly the impact of interactions between the pituitary and ovary on reproduction and fertility regulation and the impacts of ageing, including menopause.
- The role of steroid hormones and their interactions with intracellular nuclear receptors (regulators of gene expression) in the development, treatment and prevention of serious health challenges, including breast cancer and cardiovascular disease.
- The molecular oncology of endocrine cancers, including those of the breast, ovary and thyroid, as well as the development of novel treatments for these cancers.
- Genetics of male infertility – We are researching the importance of DNA changes, genetic instability and epigenetic imprinting as causes of male infertility.
- Developing new reversible male contraceptives – Sex hormone treatment is a promising reversible contraceptive that acts by stopping the pituitary hormone drive needed for sperm production.
- Testosterone and cardiometabolic health – Androgen physiology and the role of testosterone in ageing and metabolism are a major focus of the team's work, with several clinical interventional studies looking at a range of endpoints, including body composition, cardiovascular risk and quality of life.

Research Group Heads

Steroid Receptor Biology: Professor Peter Fuller

Cardiovascular Endocrinology: Dr Morag Young

Metabolic Bone Research: Dr Frances Milat

Clinical Andrology: Professor Robert McLachlan

RESEARCH GROUP: Steroid Receptor Biology

29. Mineralocorticoid receptor regulation of gene expression in ovarian tissue

Theme: Endocrinology

Suitability: Honours, PhD

Project Leaders: Prof Peter Fuller, Dr Ann Drummond

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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 ovarian tissue in vitro and in vivo. The role of this receptor in the ovary and in ovarian cancer is emerging as a potentially important story, since the MR may influence differentiation and apoptosis during ovarian folliculogenesis; such changes are likely to have consequences for fertility and ovarian cancer development. We have created a tissue-specific knockout mouse to investigate the impact of MR loss on ovarian tissue development and function, and we have ovarian cancer cell lines we can manipulate to evaluate the signalling mechanisms involved. Insights gained from these studies will lead to the development of new therapeutic agents to better treat these conditions.
Keywords: mineralocorticoid, ovary, knockout

30. Mineralocorticoid receptor regulation of gene expression in mammary tissue

Theme: Endocrinology

Suitability: Honours, PhD

Project Leaders: Prof Peter Fuller, Dr Ann Drummond

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Phone: 03 8572 2535, 03 8572 2548

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 tissue in vitro and in vivo. The role of this receptor in the breast and in breast cancer is emerging as a potentially important story, given that the 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 tissue development and function, and we have breast cancer cell lines we can manipulate to evaluate the signalling mechanisms involved. Insights gained from these studies may lead to the development of new therapeutic agents for breast cancer treatment.
Keywords: mineralocorticoid, mammary tissue, knockout

31. Structure-function relationships of the mineralocorticoid receptor

Theme: Endocrinology

Suitability: Honours, PhD

Project Leader: Prof Peter Fuller

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Phone: 03 8572 2535

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. Understanding these interactions and their structural basis will lead to the development of new therapeutic agents. The studies will involve the use of yeast-2-hybrid screens, transactivation assays, structural analysis, mutation detection, comparative biology and transgenic mouse models.
Keywords: mineralocorticoid, aldosterone, cortisol

32. Role of XIAP in normal ovarian folliculogenesis

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Simon Chu, Dr Ann Drummond

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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: apoptosis, folliculogenesis

33. Role of XIAP in endocrine cancer (ovarian and thyroid)

Theme: Cancer

Suitability: Honours, PhD

Project Leaders: Dr Simon Chu, 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 anti-apoptotic 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 as well as 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 preclinical, proof-of-concept approach for translation to the clinic.
Keywords: apoptosis, therapeutic

34. Molecular pathogenesis of granulosa cell tumours of the ovary

Theme: Cancer

Suitability: Honours, PhD

Project Leaders: Dr Simon Chu, Prof Peter Fuller

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Phone: 03 8572 2545, 03 8572 2535

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 and microRNA analyses. Other studies explore the role of nuclear receptors, including estrogen receptor-beta and peroxisome proliferator-activated receptor-gamma, and of genes that we have identified as being overexpressed in advanced disease with a view to developing novel therapeutic strategies.
Keywords: granulosa cell, tumour, therapeutic

35. Hormonal regulation of folliculogenesis

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leader: Dr Ann Drummond

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Project Description: The mechanisms by which hormones and locally produced ovarian factors interact to regulate ovarian functions remain unclear. One of our interests involves estrogen and the genes it activates via estrogen receptor beta (ERβ), to exert its effects on ovarian growth and differentiation. We plan to identify genes and proteins specifically activated by ERβ and elucidate their biological role in ovarian function. Our goal is to elucidate the mechanisms responsible for the local control of ovarian follicular development in order to obtain a better understanding of, and treatments for, infertility, premature menopause and ovarian cancer.
Keywords: ovarian, follicular

RESEARCH GROUP: Cardiovascular Endocrinology

36. Nuclear receptor co-regulators in heart disease and inflammation

Theme: Cardiovascular

Suitability: Honours, PhD

Project Leader: Dr Morag Young

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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 screen to identify novel MR co-regulators in macrophages, followed by 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

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

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, PhD

Project Leader: Dr Morag Young

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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

38. Identification of mineralocorticoid receptor signalling pathways in macrophages: a role in heart disease

Theme: Cardiovascular

Suitability: Honours, PhD

Project Leader: Dr Morag Young

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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. It is also present in various non-epithelial cell types, including cardiac myocytes, vascular smooth muscle, brain and immune cells such as macrophages. In these cells, the actions of the MR are not fully 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 is not fully 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. The recent identification of the cardioprotective effects of macrophage-specific deletion of the MR provides supportive evidence for targeted therapeutics specifically designed for macrophages for the treatment of cardiac failure and hypertension. Previous data from the host 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 goal of this project is to define and characterise these pathways. In this way, we hope to identify novel mechanisms of heart disease that may also apply to other diseases.
Keywords: heart disease, mineralocorticoid receptor, macrophage

39. A search for new biomarkers and therapeutic targets in heart failure

Theme: Cardiovascular

Suitability: Honours, PhD

Project Leader: Dr Morag Young

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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 hormones aldosterone and cortisol may play a key role in heart muscle deterioration by activating the mineralocorticoid receptor (MR). Patients with high blood pressure caused by primary aldosteronism (PA) have excessive aldosterone in their blood and are particularly at risk of heart failure. Drugs that block the MR will block the effect of these hormones, and therefore improve heart failure. However, these drugs can cause salt imbalance in the blood because they

also block MR in the kidney, which is important for salt handling. In addition, treatment for heart failure is often delayed as early heart failure is difficult to diagnose with non-specific symptoms of fatigue and shortness of breath. There is no simple blood test to diagnose heart failure. By studying circulating blood cells in patients with heart failure or PA before and after they are treated with MR blockers, this research hopes to detect 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 that do not cause kidney-related side effects.
Keywords: mineralocorticoid receptor, macrophage, heart failure

40. Understanding the signalling mechanisms for mineralocorticoid receptor regulation of cardiomyocyte function in heart disease

Theme: Cardiovascular

Suitability: Honours, PhD

Project Leader: Dr Morag Young

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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. New studies 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 are directly investigating using in vivo and in vitro models to determine their regulation by the 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.
Keywords: heart failure, mineralocorticoid receptor

41. Evaluating the prevalence of primary aldosteronism (PA) in the community

Theme: Cardiovascular

Suitability: Honours, BMedSci, PhD

Project Leader: Dr Jun Yang

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Project Description: Primary aldosteronism is the most common, and potentially curable, cause of hypertension, estimated to affect 5-10% of all hypertensive patients. It leads to greater cardiovascular injury than hypertension alone. However, it is currently under-diagnosed due to complexity of diagnosis and lack of uniform guidelines. Building upon our expertise in the diagnosis and management of PA at Monash Health, we will recruit newly diagnosed hypertensive patients from an unselected general practice population and evaluate the prevalence of PA in this cohort. The prevalence of associated comorbidities such as ischaemic heart disease, cerebrovascular disease and cardiac arrhythmias will also be evaluated. Blood and urine samples from these patients will undergo laboratory analysis to identify novel biomarkers of PA. This project has the potential to change management guidelines for hypertension and optimise the diagnosis of PA so that patients receive the most effective therapy for their hypertension.
Keywords: primary aldosteronism, hypertension, endocrine hypertension, aldosterone

RESEARCH GROUP: Metabolic Bone Research

42. Osteoporosis and metabolic bone disorders

Theme: Endocrinology

Suitability: Honours, PhD

Project Leader: Dr 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 chronic neurological disability, understanding osteoporosis in haemoglobinopathies, assessing risk factors for atypical femoral fractures, the evaluation and management of mineral and bone disorders in chronic kidney disease, and metabolic bone disorders in pregnancy. Research projects are available in many of these clinical areas.
Keywords: bone disorder, osteoporosis

RESEARCH GROUP: Clinical Andrology

43. Male fertility and infertility

Theme: Men's Health

Suitability: BMedSci, PhD

Project Leader: Prof Robert McLachlan

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Phone: 03 8572 2502

Project Description: We are investigating several areas of men's reproductive health. We have studies underway looking at genetic instability and epigenetic imprinting as causes of male infertility. We are researching the development of new reversible male contraceptives involving sex hormone treatment to stop sperm production.
Keywords: infertility, sex hormones, contraceptives

44. Men's health

Theme: Men's Health

Suitability: BMedSci, PhD

Project Leader: Prof Robert McLachlan

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Project Description: We are investigating the role of testosterone in ageing and metabolism, including cardiac health, with several clinical interventional studies looking at a range of endpoints, including body composition, cardiovascular risk and quality of life.
Keywords: androgen, ageing

CENTRE FOR GENETIC DISEASES

Centre Head: Professor Justin St. John

Many of the diseases that affect us originate from changes present at or just after fertilisation and are known as inherited disorders. It was originally thought that these diseases were primarily caused by mutations to the genes inherited from our parents. However, it is becoming increasingly evident that many diseases also arise from the number of copies of a gene present in our cells and the changes to epigenetic regulators, which are factors that control how and if the gene is expressed.

By looking into the very earliest stages of development, when genetic and epigenetic disorders first manifest, we can understand the underlying mechanisms of disease and provide a platform for the development of tomorrow's therapies and clinical practices.

The Centre for Genetic Diseases studies the inheritance of mutations, the number of copies of genes and epigenetic regulators of gene expression. Our aim is to provide explanations for how a large number of diseases are passed from one generation to the next.

The Centre investigates how very early epigenetic markers in sperm and eggs are controlled during development, and how they will affect our children, and their children, if they are poorly regulated.

Researchers are developing technologies to increase the number of crucial disease-protecting mitochondrial DNA in the eggs of women deficient in mitochondrial DNA. Eggs with low mitochondrial DNA copy number are predisposed to develop diseases such as obesity and diabetes.

Another research focus is how faults in mitochondrial proteins cause energy generation defects that result in mitochondrial disease.

Research Groups and Heads

Mitochondrial Genetics: Prof Justin St. John

Molecular Basis of Mitochondrial Disease: Dr Matthew McKenzie

Germ Cell Development and Epigenetics: Dr Patrick Western

RESEARCH GROUP: Mitochondrial Genetics

45. Understanding the regulation of mitochondrial DNA copy number in undifferentiated and differentiating embryonic stem cells

Theme: Genetic Diseases

Suitability: Honours, PhD

Project Leader: Prof Justin St. John

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Project Description: Mitochondrial DNA (mtDNA) encodes key genes associated with the cell's major energy-generating process, oxidative phosphorylation, which takes place in the electron transfer chain. Little is known about how mtDNA copy number is regulated during cellular differentiation and how specialised cells acquire specific numbers of mtDNA to meet their requirements for cellular energy. This project aims to define this process using undifferentiated and differentiating embryonic stem cells. Along with learning stem cell culture, you will use real-time PCR, western blotting, immunocytochemistry, confocal microscopy, and siRNA and expression vectors to downregulate and overexpress key genes associated with mtDNA replication.
Keywords: mitochondria, mtDNA, oxidative phosphorylation, differentiation

46. Defining the role played by mitochondrial DNA in fertilisation outcome

Theme: Genetic Diseases

Suitability: Honours, PhD

Project Leader: Prof Justin St. John

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Phone: 03 8572 2678

Project Description: Mitochondrial DNA plays a critical role in fertilisation and early development. Eggs with low mitochondrial copy number often fail to fertilise. However, these eggs can be

rescued by supplementing them with autologous populations of mitochondria carrying mitochondrial DNA. Little is known about how mitochondrial DNA copy number can alter fertilisation and developmental outcomes. This project aims to define the processes using a pig embryology model and state-of-the-art next generation sequencing approaches to identify the key gene pathways and gene regulators involved. Along with learning egg culture and fertilisation techniques, you will use real-time PCR, next generation sequencing and bioinformatics.
Keywords: mitochondria, mtDNA, genetics, fertilisation

RESEARCH GROUP: Molecular Basis of Mitochondrial Disease

47. The assembly of mitochondrial protein complexes and defects in human disease

Theme: Genetic Diseases

Suitability: Honours, PhD

Project Leaders: Dr Matthew McKenzie, Prof Justin St. John

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Project Description: Mitochondria oxidise sugars and fats by oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to generate energy for the cell. Defects in either of these biochemical pathways can result in mitochondrial disease, which in many cases is fatal at an early age. This project will use cells from patients with mitochondrial disorders to investigate how defects in OXPHOS and FAO proteins cause disease. Induced pluripotent stem (iPS) cells will be created from these patient cells and differentiated to examine mitochondrial dysfunction in neurons and cardiomyocytes. In addition, gene targeting tools will be used to create knockout FAO human embryonic stem cell lines for differentiation and analysis. Techniques such as Blue Native-PAGE, confocal microscopy, in vitro mitochondrial import and stem cell culturing will be employed throughout the project.
Keywords: mitochondria, mitochondrial disease, protein complexes, iPS cells, native gel electrophoresis, oxidative phosphorylation, fatty acid oxidation

48. MicroRNA regulation of mitochondrial function

Theme: Genetic Diseases

Suitability: Honours, PhD

Project Leaders: Dr Matthew McKenzie, Dr Michael Gantier

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Project Description: Mitochondria generate most of the energy needed for normal cell function; however how the cell controls this process is largely unknown. This project will examine how microRNAs control mitochondrial metabolism and how this regulation is coordinated with other functions within the cell. It will utilise techniques such as Blue Native-PAGE, transfection of mammalian cells with synthetic microRNAs, high throughput oxygen flux analysis and quantitative real-time PCR to examine how microRNAs coordinate mitochondrial metabolism with the regulation of global cell function.

Keywords: mitochondria, metabolism, microRNA regulation, oxidative phosphorylation, native gel electrophoresis

RESEARCH GROUP: Germ Cell Development and Epigenetics

49. Pharmaceutical impacts on germline epigenetics and offspring health and development

Theme: Genetic Diseases

Suitability: Honours, PhD

Project Leader: Dr Patrick Western

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Project Description: Germ cells are specialised cells found in the developing testes and ovaries that form sperm in males, or oocytes (eggs) in females. Sperm and oocytes transmit the parent's genetic and epigenetic information to the offspring. Epigenetic modifications to the chromatin (DNA plus the proteins that package it) provide a long-term 'directory' or 'memory' of which genes should be switched on or off in each cell, and thereby underpin cell identity and organ function. Conversely, disrupted epigenetic states occur in diseases including cancer, metabolic and behavioural disorders.

Importantly, epigenetic modifications are reversible in normal cells, allowing gene activity to be changed when necessary. This occurs most extensively in developing germ cells in which epigenetic information is re-set to equip the sperm and oocyte with the appropriate epigenetic information for directing embryonic and postnatal development in the offspring.

Significantly, epigenetic programming is susceptible to alteration by environmental influences such as chemicals, diet and drugs. Altered epigenetic states can be transmitted to the next generation and affect health and development in the offspring. Such changes contribute to the developmental origins of health and disease (DOHaD) in a parent's offspring.
The Germ Cell Development and Epigenetics group aims to improve understanding of epigenetics in the germ cells and the effects of epigenetic change on the offspring. Specifically, we use gene mutations and drugs to disrupt epigenetic modifier function in mouse germ cells to determine: (i) the function of specific epigenetic modifiers in germ cell development; and (ii) the ability of germ cells with altered epigenetic states to direct development in the parent's offspring.

New therapeutic drugs that target epigenetic mechanisms are being used to treat an increasing number of diseases, including cancer. Whether these drugs alter germline epigenetics and potentially the inheritance of epigenetic information remains unknown.

This project will examine how epigenetic modifying drugs impact germ cell development and the patterning of epigenetic information in the germline. Using organ culture and in-vivo drug dosage in mice, we will challenge developing germ cells with specific epigenetic modifying drugs. Outcomes for germ cell development and epigenetics will be measured using immunofluoresence, qRT-PCR and flow cytometry.

This project will determine whether pharmaceuticals that inhibit epigenetic modifying enzymes alter the patterning of epigenetic information in the germline and how this impacts on health and developmental outcomes in offspring. Understanding these processes is essential to understand how epigenetic information in the parent affects development in the offspring.

Techniques: Mouse models, organ culture, qPCR, immunofluorescence, advanced micro-imaging (e.g. confocal microscopy), flow cytometry.

Keywords: epigenetics, reproduction, germ cells, inherited disease, pharmaceuticals

50. Epigenetic regulation of tumour cell death

Theme: Genetic Diseases

Suitability: Honours

Project Leader: Dr Patrick Western

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Project Description: Epigenetic mechanisms control how genes are switched on and off in cells over long periods of time. Importantly, epigenetic modifications to the DNA are heritable between cells and maintain cell identity and function throughout life. These mechanisms are commonly disrupted in cancer cells.

Almost half of an individual's DNA is made from viral DNA sequences that have invaded our cells over many thousands of years and remain present, but dormant in all cells. These sequences are known as retrovirally derived transposable elements (RTEs). Under certain conditions some RTEs can be reawakened in cells. Recent work has shown that this occurs during treatment of some cancers and ultimately leads to death of the affected cancer cells and disease control.

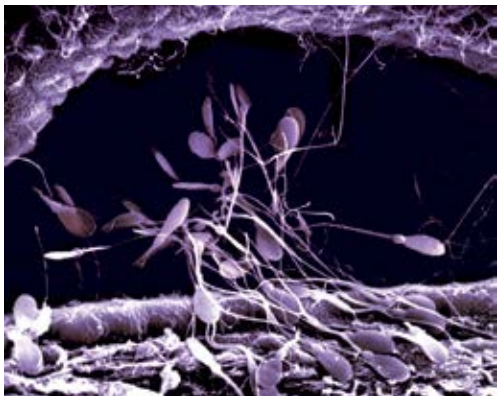
Particular mechanisms act in our cells to prevent the incorrect activation of these virally derived RTE sequences in our DNA. Our research and that of other groups has shown that a particular repressive epigenetic mechanism called histone methylation, normally prevents expression of RTEs in the cells that will form sperm and eggs. These discoveries reveal an important function for this epigenetic mechanism in controlling RTEs.

Other new studies have shown that some RTEs can be awakened in cancer cells using a drug that blocks a different epigenetic modification called DNA methylation. Crucially, after they are reawakened, RTEs are seen as virally derived by the human immune system. This leads the immune system to attack the cancer cells, causing tumour regression.
This provides an exciting new understanding of how this drug causes cancer regression. However, many patients remain resistant and the treatment remains ineffective.

This project will explore how epigenetic mechanisms repress RTEs in cancer cells and whether specific treatments lead to their activation. Experiments will involve the treatment of a range of cancer cells types using drugs that block enzymes that regulate epigenetic modifications. The cells will be analysed for a range of key responses to the drug treatments using flow cytometry, immunofluorescence, western blotting, and a range of advanced molecular and cell biology techniques.

This work seeks to improve our understanding of epigenetic mechanisms in cancer, with the ultimate aim of improving patient treatment. Development of more effective new cancer treatments will benefit cancer patients and their families, and will reduce the burden of disease on our health system.

Keywords: epigenetics, cancer, pharmaceuticals, cell death



CENTRE FOR INNATE IMMUNITY AND INFECTIOUS DISEASES

Centre Head: Professor Paul Hertzog

The Centre for Innate Immunity and Infectious Diseases (CiiiD) researches the molecular regulation of the innate immune response, and its impact on disease. Our understanding of the innate immune response has undergone a revolution in recent years. We now appreciate that this early immune response determines how the body responds to infection or the presence of cancer cells, for instance by providing immediate protection and sculpting the ensuing adaptive (sustained) immune responses.

In addition, innate immunity can initiate the inflammatory response and modulate the development of chronic inflammatory and autoimmune diseases, as well as inflammation-associated cancers. Our aim is to understand the molecular pathways that regulate these disease processes as well as their normal physiological roles. In this way, CiiiD scientists aim to develop new approaches to prevent, diagnose and treat: i) infections such as influenza, HIV and chlamydia; ii) inflammatory diseases such as gastritis and chronic obstructive pulmonary disease; and iii) cancers of the stomach, lung, pancreas, breast and reproductive tract.

Staff and students working in CiiiD have collective multidisciplinary expertise in molecular biology, signal transduction, protein interactions, cell biology, immunology, oncology, infectious disease, functional genomics and bioinformatics, and transgenic techniques for generating and characterising gene knockout and transgenic mice as models of human disease. The multidisciplinary teaching and training environment within CiiiD provides students with a range of skills in biomedical research that will be recognised internationally for a research career. The Centre trains UROP, Honours, Masters and PhD students from backgrounds in science, biomedical science, medicine and health informatics, and more diverse backgrounds for those interested in applying computational and mathematical skills to solving biomedical problems. CiiiD is committed to providing a nurturing environment and a strong work ethic to optimise each student's experience. CiiiD is one of the largest centres for innate immunity in Australia, bringing in approximately $3M in grant funding per annum and publishing nearly 100 peer-reviewed publications in the past three years, including works in prestigious journals such as Nature, Science, Nature Immunology, Immunity, the Journal of Clinical Investigation, Nature Medicine and Cancer Cell.

Research Disciplines:

- Biochemistry
- Immunology
- Microbiology
- Physiology
- Genetics
- Computational Biology

Research Group and Heads

Regulation of Interferon and Innate Signalling: Prof Paul Hertzog

Cancer and Immune Signalling: Prof Brendan Jenkins

Gastrointestinal Infection and Inflammation: A/Prof Richard Ferrero

Pattern Recognition Receptors and Inflammation: Dr Ashley Mansell

Nucleic Acids and Innate Immunity: Dr Michael Gantier

Host-Pathogen Interactions: Dr Maria Kaparakis-Liaskos

Respiratory and Lung Research: Prof Philip Bardin

RESEARCH GROUP: Regulation of Interferon and Innate Signalling

51. Systems biology of innate immune signalling

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Prof Paul Hertzog

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Project Description: In the process of studying the complexities of signal transduction, we generate copious data from microarray and next generation sequencing of the transcriptome activated by pathogens and by interferons. In order to help analyse the pathways and functional gene clusters involved and how they are integrated, we have a computational biology group working on the generation of 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. These in silico studies are complemented and validated by 'wet' lab experiments, including gene regulation and chromatin IP. Specific projects include:

- Analysis of IFN 'signatures' in disease (infections, inflammation, autoimmunity, cancer)
- Discovery of novel signalling pathways by promoter analysis
- MicroRNA regulation of IFN regulated genes
- Whole genome (RNA Seq) analysis and integration of IFN signalling.

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

52. Innate immune responses regulating breast cancer metastases

Theme: Cancer; Infectious and Inflammatory Diseases; Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Paul Hertzog, Dr Helen Cumming

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Project Description: The mechanisms that regulate the process of metastases of breast cancer to distant organs such as lungs and bone are not understood, and accordingly the treatment of this disease process and prognosis of the disease are poor. Our studies use a murine model of breast cancer metastasis in collaboration with Dr B Parker at the Latrobe Institute of Molecular Sciences. We have compared primary and metastatic cancer cells by gene expression microarrays to determine the genes and their regulatory pathways that are activated or suppressed. This has led to the discovery of a novel epithelial innate immune pathway that is suppressed in metastases; the reversal of which reduces bone metastases significantly and increases metastases-free survival. Ongoing studies include determining the mechanisms of suppression, the effector molecules that block the metastatic process, the role of the immune response in regulating this process and clinical studies of these pathways in human samples. This research will potentially lead to new diagnostics and adjunct therapeutics and was recently published in Nature Medicine, 2012 Aug; 18(8):1224-31.
Keywords: women's health, cancer, innate immunity, bioinformatics, signal transduction

53. Characterisation of a novel cytokine in mucosal immune responses to infections

Theme: Infectious and Inflammatory Diseases; Cancer; Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Paul Hertzog, Dr Nollaig Bourke

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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, interferon epsilon (IFNε) 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 IFNε gene expression,
- Biochemistry - characterising the mechanism of IFNε interaction with receptors and activation of novel signalling pathways,
- Immunology - determining how and which immune cells are regulated in the mucosa of the female reproductive tract during infections and other disease,
- Infectious Diseases (clinical and animal models) - determining whether hormonal regulation of IFNε 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 IFNε in the development and progression of uterine and ovarian cancer.

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

54. Interferon epsilon in the human gut

Theme: Infectious and Inflammatory Diseases; Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Paul Hertzog, Dr Edward Giles

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Project Description: This project would involve working in the Hertzog lab, an internationally recognised lab with a very successful publication record. The lab recently discovered a novel type I interferon, interferon epsilon. This was found to be predominantly expressed in the female genitourinary tract and had important antiviral and antibacterial properties. More recently, it has also been identified in the colon of macaques and there is unpublished data to show its expression in the human colon. This project would therefore be to assist in the detection - initially by immunohistochemistry and PCR techniques - of interferon epsilon in the human colon. This work would lead on and be related to other studies looking at the function of this protein in controlling infection and inflammation in the gut.
Keywords: immunology, infectious diseases, innate immunity, inflammatory diseases, gastric disease

55. The role of microRNAs in modulating innate immune responses during virus infections

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Michelle Tate

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Phone: 03 8572 2742

Project Description: Influenza viruses are associated with acute respiratory illness and are responsible for millions of human deaths annually. The innate immune system provides a critical first line of defence following influenza virus infection; however, excessive

inflammation is associated with severe influenza virus infections of both mice and humans. Understanding how the innate immune system responds to influenza virus is of great importance and may provide insight as to why particular influenza virus strains induce severe disease. Host microRNAs have been shown to modulate innate immune responses. This project aims to examine the regulation of novel microRNAs in the lung following influenza virus infection and their role in controlling innate immune responses. Understanding how microRNAs modulate inappropriate or damaging immune responses is of great significance for reducing mortality and morbidity associated with influenza.
Keywords: innate immunity, viral disease, influenza, inflammation, microRNAs

56. Structural-functional characterisation of type I interferon receptors and signalling pathways

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Nicky de Weerd

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Project Description: The type I interferons (IFNs) are cytokines pivotal to the host innate immune response, which protects against viral and bacterial infections and cancer. Up to 20 different ligands share the same heterodimeric receptor. Work in our laboratory focuses on investigating the structure and function of the different type I IFNs (including the IFNα family, IFNβ and IFNε) and how they engage their receptors to activate signal transduction pathways and thus, the transmission of differential signals. This project involves the use of biochemical techniques for the purification of recombinant forms of the IFNs and their receptors, and will include such biophysical techniques as native gel electrophoresis, CD spectra, surface plasmon resonance, X-ray crystallography, proteomics and transcriptomics to characterise ligand-receptor interactions, protein-protein interactions and protein activation, and gene expression analysis to characterise signalling and biological outcomes. Aspects of this ongoing work were recently published in Nature Immunology, 2013 Sep; 14(9):901-7.
Keywords: innate immunity, protein techniques, signal transduction, structural-functional characterisation

57. The role of a novel cytokine in endometrial and cervical cancer

Theme: Cancer; Infectious and Inflammatory Diseases; Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leader: Dr Nollaig Bourke

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Project Description: Cervical and endometrial cancers are major human diseases with unmet medical needs. We have recently discovered a new interferon designated interferon epsilon (IFNε), which is highly expressed constitutively in the female reproductive tract and regulated by hormones. IFNε belongs to a cytokine family that regulates the development of cancers by direct effects on cell proliferation, survival and migration, as well as by indirect effects of activating innate and adaptive anti-tumour immunity. Aspects of this project will utilise preclinical models of these diseases, in vitro cell biology and molecular genetics approaches to examine the effects of IFNε in the development and/or therapy of endometrial and cervical cancers.
Keywords: cancer, immunity, novel therapeutics, reproductive health, anti-tumour responses

58. The role of innate immune responses in modulating disease during influenza virus infections

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Michelle Tate

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Phone: 03 8572 2742

Project Description: Innate immune responses elicited during infection with influenza viruses play an important role in modulating disease. Understanding how the innate immune system responds to different strains of influenza virus is of great importance and may provide insight into the mechanisms involved in the development of disease. This project aims to examine pathways involved in the induction of inflammation using both in vitro and in vivo models of influenza virus infection. Understanding how microRNAs modulate inappropriate or damaging immune responses is of great significance for reducing mortality and morbidity associated with influenza.
Keywords: innate immunity, viral disease, influenza, inflammation

59. The role of type I interferon receptors in modulating pulmonary inflammation in vivo

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Michelle Tate

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Phone: 03 8572 2742

Project Description: Pulmonary hyperinflammation and dysregulated production of potent pro-inflammatory cytokines such as interleukin-1β are associated with severe and fatal infections involving viruses, such as influenza A virus, as well as a number of lung diseases. The importance of type I interferons (IFNs) in infection and immunity has been well documented in vivo and they are classically known for their immunomodulatory and antiviral effects, elicited following binding to their cell surface receptors, Ifnar1 and Ifnar2. However, the role of each IFN receptor in regulating inflammation and disease in vivo has not been well characterised. This project will elucidate the mechanisms involved in IFN receptor-mediated regulation of inflammation using in vitro and in vivo models. Understanding the pathways involved in regulating inflammation is of significant importance for the understanding of disease pathogenesis and the design of new therapeutics.
Keywords: innate immunity, inflammation, regulation, disease pathogenesis

RESEARCH GROUP: Cancer and Immune Signalling

60. Identification of novel immune regulators in stomach inflammation and cancer

Theme: Cancer; Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Prof Brendan Jenkins

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Project Description: Bacterial infection with Helicobacter pylori is associated with stomach inflammation (gastritis), which can also progress to stomach cancer. However, it remains largely unknown how Helicobacter triggers these gastric diseases in people. Using a mouse model that spontaneously develops gastric inflammation and tumours, our aim is to identify and understand how novel immune regulators (e.g. inflammasomes, cytokine signal transducers such as STAT3) in the stomach trigger chronic inflammatory responses that lead to gastric cancer. This project encompasses a wide range of molecular and cell biological and genetic approaches to better understand how uncontrolled cytokine signal transduction leads to chronic activation of the immune system and ultimately stomach cancer.

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

61. Role of Toll-like receptors in stomach cancer

Theme: Cancer; Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Prof Brendan Jenkins

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Project Description: Toll-like receptors (TLRs) are key molecules of the innate immune system that recognise microbial-derived products to trigger the inflammatory response. Recently, however, we and others have identified that 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 members of the TLR family promote stomach cancer. Such research will ultimately assist in identifying genes that could be used as biomarkers for screening/early detection of stomach cancer, and also targets, for the design of therapeutic treatment strategies.

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

62. Identification of interleukin-6 signalling as a therapeutic target in emphysema/COPD and lung cancer

Theme: Cancer; Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Prof Brendan Jenkins

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Project Description: Interleukin-6 (IL-6) has been implicated as a causative factor in both emphysema and lung cancer, the latter 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. This project aims for the first time to define an alternative IL-6 signalling pathway, termed 'trans-signalling', in the molecular pathogenesis of lung diseases (emphysema and cancer) by employing a combination of in vivo lung emphysema and cancer mouse models, human lung cell lines and clinical biopsies.

Keywords: cancer, lung disease, signal transduction

63. Inflammasome in lung diseases

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Saleela Ruwanpura

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Project Description: Growing evidence indicates that the inflammasome (an intracellular protein complex that regulates the maturation and release of pro-inflammatory cytokines of the interleukin-1 family in response to pathogens and endogenous danger signals) plays a key role in the pathogenesis of lung diseases, such as chronic obstructive pulmonary disease (COPD), a condition predicted to be the third-leading cause of death worldwide by 2020. Using novel cell/molecular biology methodologies, gene-deficient mouse models and human clinical biopsies/serums, we will understand the mechanism of inflammasome signalling in COPD pathophysiology, and this will lead to new therapeutic approaches. This project offers the opportunity to interact with our collaborators in the University of Melbourne.

Keywords: inflammasomes, lung diseases, signal transduction, biomarkers

RESEARCH GROUP: Gastrointestinal Infection and Inflammation

64. The role of NOD1 sensing in cell survival responses favouring Helicobacter pylori survival

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: A/Prof Richard Ferrero

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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 pro-inflammatory signalling cascades. We have preliminary data suggesting that host-adapted Helicobacter pylori strains exhibit different muropeptide forms to induce NOD1 inflammatory responses in the host. This project will test the hypothesis that modulation of muropeptide composition is a strategy used by H. pylori to actively engage the NOD1 signalling pathway, thereby initiating host cell responses that favour bacterial survival in vivo. In some hosts, these responses may favour the development of gastric cancer. This project will involve a variety of techniques, including primary cell culture, mouse infection, histology, cytokine ELISA and qPCR.
Keywords: innate immunity, infection, signal transduction, gastric disease, cancer

65. Regulation and biological functions of a novel NLR protein, NLRC5

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: A/Prof Richard Ferrero

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Project Description: The NLR family member, NLRC5, was first described in 2008. Although the functions of NLRC5 are still poorly understood, it is now clear that this protein is activated in response to interferon-γ and plays a role in MHC class I presentation. Our laboratory has the first evidence suggesting that NLRC5 may play an important role in regulating inflammation in response to chronic Helicobacter pylori infection. Specifically, we have shown that conditional Nlrc5-deficient mice, in response to chronic Helicobacter infection, exhibit an accelerated formation of B cell mucosa-associated lymphoid tissue (MALT) in the stomach, consistent with the early stages of gastric MALT lymphoma. The overall aims of the project are to investigate how NLRC5 prevents B cell lymphomagenesis in response to 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 Nlrc5-deficient mice. The project will involve various techniques, such as primary cell culture, mouse infection, histology, flow cytometry, cytokine ELISA and qPCR.
Keywords: innate immunity, infection, signal transduction, gastric disease, cancer, MALT lymphoma

66. Innate immune properties of bacterial membrane vesicles

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: A/Prof Richard Ferrero

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Project Description: The release of small membrane vesicles (MVs) is a property that has been conserved by both multi- and unicellular organisms during evolution. One of the major functions of these MVs is to facilitate intercellular communication and transport of molecules. The release of outer MVs by prokaryotes was first described nearly 40 years ago, yet the biological significance of these structures is only beginning to be appreciated. We have previously shown that MVs from Gram-negative bacteria are potent modulators of host immune responses. The aim of the project is to investigate the immunogenic properties of Gram-negative MVs in vivo using zebrafish and mouse models. These models will be used to image MV interactions with innate immune cells and to characterise the adaptive immune responses induced by MVs, respectively. This project will involve a variety of techniques, including cell culture, zebrafish and mouse models, fluorescence imaging, flow cytometry, cytokine ELISA and qPCR.
Keywords: innate immunity, infection, haematopoiesis, zebrafish

67. The role of a novel Helicobacter pylori virulence factor in regulating host immune responses

Theme: Infectious and Inflammatory Diseases

Suitability: Honours

Project Leader: A/Prof Richard Ferrero

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Project Description: A major virulence determinant of Helicobacter pylori is a type IV secretion system, encoded by the cag pathogenicity island (cagPAI). The H. pylori T4SS interacts intimately with host epithelial cells and delivers factors to these cells, resulting in the induction of oncogenic and pro-inflammatory signalling cascades. Studies have shown that cagPAI+ H. pylori strains with a functional T4SS are associated with more severe disease than cagPAI- strains. Thus, H. pylori strains harbouring a cagPAI are generally thought to be more virulent. We have identified a cagPAI-encoded factor, however, that can restrict or modulate host responses, thus facilitating establishment of a chronic infection. Microarray studies on gastric biopsies from mice that had been infected with H. pylori wild type or bacteria lacking this factor identified the upregulation of several long non-coding RNAs (lncRNAs). The aim of the work is to confirm the regulation of these lncRNAs and thus determine the mechanisms whereby this H. pylori factor may dampen host immune responses. This project will involve molecular biology techniques (i.e. cloning, PCR, sequencing), cell culture and mouse infection studies, cytokine ELISA and qPCR.
Keywords: microbiology, infectious disease, molecular biology, long non-coding RNA

RESEARCH GROUP: Pattern Recognition Receptors and Inflammation

68. Regulation of pattern recognition receptor signalling in mouse models of inflammatory disease

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Ashley Mansell

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Project Description: We have recently generated mice expressing a human single nucleotide polymorphism of TLR2 and TLR4 adaptor protein Mal (termed Mal D96N). Using this model of human disease, we will explore inflammatory disease models in this mouse using bacterial infection. We have also generated a mouse deficient in the gene MUL1, which we have previously demonstrated has a role in modulating antiviral immune responses. We also have projects examining the regulation of inflammation in viral models of infections. (E. coli, LPS, influenza A, EMCV, dengue and Sendai virus). Keywords: innate immunity, Toll-like receptors, Pattern Recognition Receptors, inflammation, cell biology

69. The inflammasome and hyperinflammation in emerging infectious diseases

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leader: Dr Ashley Mansell

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Project Description: We recently identified and characterised aggregated viral proteins as a novel class of inflammasome activators that induce hyperinflammation characteristic of infections such as avian influenza. We have now identified several proteins that show aggregating potential and inflammasome activation in viruses characterised by excessive inflammation, such as Ebola virus, SARS-coronavirus, dengue virus and picornaviruses. Using novel cell biology methodologies, cell lines, microimaging and gene-deficient mouse models, we will explore the capacity of peptides based on these viral proteins to examine inflammasome activation. This project offers the opportunity to interact with virologists and our collaborators in Bonn, Germany. Keywords: innate immunity, inflammation, emerging infectious diseases, inflammasome, infectious disease

RESEARCH GROUP: Nucleic Acids and Innate Immunity

70. Modulating microRNA levels in inflammation and cancer

Theme: Infectious and Inflammatory Diseases; Cancer

Suitability: Honours, PhD

Project Leaders: Dr Michael Gantier, Dr Jonathan Ferrand

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Project Description: We have recently uncovered a critical role for microRNAs (miRNAs) in the fine-tuning of inflammation (Gantier et al., Nucleic Acids Research, 2012). This project proposes to characterise novel strategies to therapeutically modulate the action of inflammatory miRNAs. The successful candidate will investigate novel techniques to modulate miRNA levels and control inflammation/tumourigenesis in specific target cells, in vitro and in vivo. He/she will gain cutting-edge practical knowledge in molecular, cellular and animal biology, working on a project with a strong translational angle.
Keywords: innate immunity, microRNAs, inflammation, gene expression, bioinformatics

RESEARCH GROUP: Respiratory and Lung Research

71. Characterisation of innate immune responses to virus-induced exacerbation of asthma and COPD

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leaders: Prof Philip Bardin, Dr Belinda Thomas

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Project Description: Our studies aim to understand how viruses, such as rhinovirus and influenza, cause asthma attacks. Previous studies in our laboratory (Thomas et al., Am J Resp Cell Mol Biol, 2009; Thomas et al., Sci Rep, 2014) have demonstrated that reduced innate immune responses contribute to enhanced virus infection in asthmatic persons and in a mouse model of influenza A infection. Further studies using validated primary cell culture models and various mouse models of virus infection are examining the mechanisms contributing to reduced host immune responses.
Keywords: asthma, viral disease, innate immunity, mouse models, infection

CENTRE FOR REPRODUCTIVE HEALTH

Centre Head: Professor Lois Salamonsen

Research at the Centre for Reproductive Health (CRH) is strongly based in both basic and translational science. Addressing issues in reproductive health is a key global challenge; changes within our environment and in society are strongly affecting male and female reproduction and the long-term health of our offspring.

These changes alter the manner in which pregnancies are achieved, with an increasing number of couples seeking the use of assisted reproductive technologies. Moreover, environmental and genetic alterations can detrimentally affect the early development of the embryo, impacting on the formation of the gonads and also the integrity of eggs and sperm. Further, the environment within the uterus is critical for establishing a successful pregnancy, and alterations at the time of embryo implantation can affect the development of the placenta, the fetus and the long-term health of the child.

We are also trying to establish what makes a male male and what makes a female female; critical when we consider how sex differences affect the incidence of a number of diseases (e.g. Parkinson's and attention deficit hyperactivity disorder (ADHD)), and the need to diagnose and manage children born with gender identity or intersex/DSD conditions.

With the rapidly increasing world population, new approaches are emerging in the field of infertility 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 Groups

Endometrial Remodelling – The intrauterine microenvironment of implantation; endometrial repair; embryo-maternal interactions via exosomes; tests for endometrial receptivity.

Embryo Implantation – Embryo-maternal interactions; microRNA and embryo factors; placental development; endometrial cancer.

Implantation and Placentation – Molecular changes during placentation; pre-eclampsia; post-translational changes during implantation and placentation.

Sex Determination and Gonadal Development – Genetic mechanisms underlying testis and ovary formation in the embryo; to improve diagnosis and management of patients with disorders of sex development (DSD/intersex).

Testis Development and Male Germ Cell Biology – This research explores the tightly regulated crosstalk in the fetus and newborn, which occurs between sperm precursor cells and their supporting niche cells. The goal is to identify factors that are essential for normal fertility, underpin the pathogenesis of testicular cancer and influence growth of the fetus.

Spermatozoal Development and its Control Systems – This topic impacts on male infertility and also assists in identifying potential sites of action of male contraception. Projects include studies of the hormonal and cytokine regulation of spermatogenesis, with special focus on germ cell biology, Sertoli cell junctions and minimally invasive diagnostic testing for testicular function.

Male Reproductive Immunology – Understanding immune privilege in reproductive tissues; roles of 'reproductive hormones' in the control of inflammation and tissue repair; lymphocytes and macrophages in male reproductive function.

Brain and Gender – Brain sexual differentiation and gender bias in diseases such as Parkinson's disease, ADHD and schizophrenia, towards improved therapies. Genetics of gender identity mechanisms that underpin testis development and germ cell differentiation, demonstrating key switches in the molecules that regulate cell fate decisions, most notably, relating to members of the pleiotropic TGF superfamily of ligands and, recently, Hedgehog signalling. Another focus on nuclear transport has identified a new mechanism by which spermatogenesis is regulated.

Ovarian Biology – Ovarian cancer has one of the worst outcomes of gynaecological diseases, particularly because it is diagnosed too late in its progression, and metastasis and chemoresistance are common. We are investigating the role of TIMPs, the natural inhibitors of MMPs and ADAMTS, in the progression of serous ovarian cancer in order to understand the mechanisms involved, which could lead to new targeted therapies.

Research Group Heads

Endometrial Remodelling: Prof Lois Salamonsen

Sex Determination and Gonadal Development: Prof Vincent Harley

Testis Development and Male Germ Cell Biology: Prof Kate Loveland

Endocrinology and Immunophysiology: A/Prof Mark Hedger

Embryo Implantation: A/Prof Eva Dimitriadis

Implantation and Placental Development: A/Prof Guiying Nie

Male Fertility Regulation: Dr Peter Stanton

Brain and Gender: Dr Joohyung Lee

Ovarian Biology: Prof Jock Findlay

RESEARCH GROUP: Endometrial Remodelling

72. Placental growth factor elicits an endometrium hostile to embryo attachment

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, PhD

Project Leaders: Dr Tracey Edgell, Prof Lois Salamonsen

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Project Description: We have identified that placental growth factor (PlGF), normally produced once a pregnancy is established, is elevated among infertile women. We hypothesise that PlGF competes with vascular endothelial growth factor (VEGF) to bind with the VEGFR1 receptor on cells, and elicits a state of 'false pregnancy', effectively making the endometrium hostile to an arriving embryo. This project will use ELISA to quantitate the PlGF present in uterine fluid and serum of women undergoing IVF, and evaluate with respect to previously quantitated VEGF concentrations. The project will utilise cell-based techniques of Xcelligence and spheroid attachment to examine the impact of PlGF on endometrial and trophoblast behaviour, and Luminex to examine cell signalling elicited by PlGF and VEGF alone or in combination.
Keywords: fertility, infertility, embryo, implantation

73. IL-17A effects on endometrium-embryo attachment

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leaders: Dr Tracey Edgell, Prof Lois Salamonsen

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Project Description: We have identified that interleukin 17A (IL-17A) is elevated in women undergoing assisted reproduction, and that IL-17A concentration is directly correlated with failure of an embryo to implant. In this project, we will examine whether it is the elevated hormone concentrations used in assisted reproductive technologies that are upregulating IL-17A production. The project will utilise cell-based techniques of Xcelligence and spheroid attachment, to directly examine the impact of IL-17A on endometrial and trophoblast cell behaviour.
Keywords: fertility, infertility, embryo, implantation

74. Defining uterine receptivity for embryo implantation

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leaders: Dr Tracey Edgell, Dr Jemma Evans, Prof Lois Salamonsen

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Project Description: The endometrium allows implantation of an embryo for only a few days in each menstrual cycle; if this 'receptivity' is not established, the woman will be infertile. It is also a major reason for failure of IVF. Our proteomics approach is defining the receptive endometrium and identifying discriminative markers for infertility. The functions of most markers we have identified are unknown in the endometrium; this project will use our in vitro cell culture/co-culture models for receptivity to determine functions and their importance to implantation.
Keywords: fertility, infertility, embryo, implantation

75. The role of exosomal proteins in embryo implantation

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: Prof Lois Salamonsen

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Project Description: Successful implantation and pregnancy requires synergistic development and communication between the endometrium and the blastocyst. We propose that endometrial exosomes (tiny particles containing cargo for transmission between cells) are important for embryo-maternal interactions prior to implantation. We have characterised the proteome of endometrial exosomes and its changes across the menstrual cycle. This project aims to characterise the functional role of exosomes in embryo implantation. Multiple cutting-edge technologies will be employed, including live cell imaging, cell transfection, XCelligence, and a cell culture model of embryo implantation. The successful candidate will gain a wide range of research skills, such as tissue culture, cellular and molecular biology, live imaging microscopy and flow cytometry. This project will provide insights into how the endometrium contributes to a healthy outcome of pregnancy.
Keywords: exosomes, embryo-maternal interactions, embryo implantation

76. 'Scratching' the surface

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: Dr Jemma Evans

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Project Description: An increasing number of couples are experiencing infertility and are turning to assisted reproduction (IVF and ICSI) to become pregnant. However, many couples go through multiple rounds of IVF without becoming pregnant. It has been suggested recently that 'scratching' or damaging the endometrium increases the chances of becoming pregnant in the following cycle, but there are also many opponents to this technique. This project will investigate whether the technique actually works and determine potential mechanisms underlying the proposed success of the endometrial scratch. Using menstrual fluid as a unique diagnostic fluid, this project will use flow cytometry, western immunoblotting and multiplex analysis to determine changes in the endometrium after the 'scratch' and determine whether examination of factors contained within menstrual fluid can be used as a predictor of pregnancy success.
Keywords: endometrium, IVF, pregnancy

77. The obesity epidemic and its impact on fertility

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: Dr Jemma Evans

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Project Description: It is increasingly appreciated that the general health and even the diet and BMI of the mother can significantly impact offspring health. While the signals and factors involved in maternal-fetal communication in later pregnancy timepoints are being unravelled, surprisingly little attention has been directed to the health of the maternal uterus at the time of implantation. This project will examine the uterus of lean versus obese mice (diet-induced obesity) and humans, looking at inflammation, fat accumulation and factors known to be essential for embryo implantation, at the time of uterine receptivity. This project will also examine the uterine 'secretome', determining the presence of secreted factors within the uterine cavity that are important for maternal fetal communication.
Keywords: lifestyle, diet, fertility, pregnancy, endometrium, embryo implantation

RESEARCH GROUP: Sex Determination and Gonadal Development

78. The biological basis of gender identity

Theme: Neuroscience and Psychiatry

Suitability: Honours, PhD

Project Leader: Prof 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

79. Identifying the genes responsible for disorders of sex development

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leader: Prof Vincent Harley

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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 DSD. 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 DSD: http://dsdgenetics.org/
Keywords: sex determination, genes, human genetics, disorders of sex determination

80. FGF signalling and sex reversal

Theme: Genetic Diseases

Suitability: Honours, Master by Research, Doctorate

Project Leader: Prof Vincent Harley

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Project Description: We have identified the first FGFR2 mutations in XY female sex reversed 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' Fgfr2cC342Y 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 that 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

81. Characterisation of novel gonadal targets of Sox9

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: Prof Vincent Harley

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Project Description: For the majority of DSD cases, the underlying genetic aetiology is unknown. In males, Sox9 is a critical 'hub' gene involved in sexual development. We hypothesise that the downstream targets of Sox9 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 upregulated in XY mouse testis compared to XX ovaries during development and downregulated in sex-reversed XY ovaries ablated for Sox9. We will perform detailed expression profiling in XX and XY embryonic gonad 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 determination, molecular genetics, sex differences

82. ATR-X syndrome and gonadal development

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: Prof 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) that affect 1% of all newborns. Clinical features include mental retardation, alpha-thalassaemia, and skeletal and genital abnormalities. The focus of our work is to investigate the role of ATR-X in gonadal development.
Keywords: sex determination, ATR-X syndrome, human genetics, disorders of sex development

83. SRY: a risk factor for Parkinson's disease in males?

Theme: Genetic Diseases

Suitability: Honours, Master by Research, Doctorate

Project Leader: Prof 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 unknown, 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 explain why males are more susceptible to PD and aim to identify SRY as a novel target for neuroprotective therapy in male PD patients.
Keywords: Parkinson's disease, brain differences, sex differences, SRY

84. How are male and female brains different?

Theme: Neuroscience and Psychiatry

Suitability: Honours, PhD

Project Leader: Prof Vincent Harley

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Project Description: Male and female brains differ in anatomy, chemistry and behaviour. The prevailing dogma that oestrogen 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 (RNA seq, ChIPseq) and rodent dissection of the substantia nigra.
Keywords: SRY, brain differences, sex differences

RESEARCH GROUP: Testis Development and Male Germ Cell Biology

85. Growth factor signalling and pathway crosstalk in testis development and disease

Theme: Women's, Children's and Reproductive Medicine; Men's Health

Suitability: Honours, Master by Research, Doctorate

Project Leader: Prof Kate Loveland

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Project Description: Many signalling pathways drive normal testis development and are essential for male reproductive health. Several projects are available in our lab to examine the functional importance of the TGFbeta, Wnt and Hedgehog signalling pathways, using cell lines, mouse models and human clinical materials. Each project will examine how communication between spermatogenic cells and their supporting somatic niche mediates cell fate decisions. These studies will focus particularly on the fetal development of gonocytes and their maturation into the spermatogonial cells, which subsequently enter meiosis and form spermatozoa. We have identified key downstream targets of these pathways, and experiments to understand their importance will reveal how these signalling pathways may contribute to testicular cancer and infertility. Analyses of transcripts, proteins and cell behaviours will be used to reveal how crosstalk between different signalling pathways governs the cellular processes that underpin fertility.
Keywords: testicular cancer, fertility, cell signalling, spermatogenesis

86. Immune cell regulation of male fertility and testicular cancer progression

Theme: Women's, Children's and Reproductive Medicine; Men's Health

Suitability: Honours, Master by Research, Doctorate

Project Leaders: Prof Kate Loveland, A/Prof Mark Hedger

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Project Description: This work will examine the vital roles of immune cells in supporting testis development, maintenance of spermatogonia required for adult fertility, and exacerbation of the pathology associated with germ cell tumours that form in young men. These experiments will examine what factors are produced by testicular immune cells to identify that they are required for normal testis development and fertility. In addition, inflammatory cells are common in established testicular tumours, and we have begun to define the key immune cells present in human testicular cancers in collaboration with colleagues at the Justus-Liebig University in Giessen, Germany and at the University of Copenhagen in Denmark. With colleagues at the Burnet Institute in Melbourne, we will employ our established model using human immune cell preparations from peripheral blood in co-culture with a human testicular cancer (seminoma) cell line. This will allow us to map how tumour and immune cells interact, so we can decipher

the crosstalk between immune cells and human germ cell tumours, and develop strategies to limit the spread of this disease that profoundly affects the reproductive health of young men. Students undertaking this project at postgraduate level may also have the opportunity to undertake 6-12 months collaborative research at the Justus Liebig University in Giessen, Germany, with the option of studying for a joint degree award from both Universities.
Keywords: testicular cancer, fertility, immune cells, cell signalling, spermatogenesis

87. Regulation of the germline and fetal organ growth by environmental cues

Theme: Women's, Children's and Reproductive Medicine; Men's Health

Suitability: Honours, Master by Research, Doctorate

Project Leaders: Prof Kate Loveland, A/Prof Eva Dimitriadis, Dr Padma Murthi

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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.
Keywords: fetal development, fertility, epigenetics, activin

RESEARCH GROUP: Endocrinology and Immunophysiology

88. Investigation of the roles of activin and follistatin in regulation of the male reproductive tract

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Mark Hedger

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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 could also include studies of the role of activin in controlling inflammation and immunity in the male tract. Students undertaking this project at postgraduate level may also have the opportunity to undertake 6-12 months collaborative research at the Justus Liebig University in Giessen, Germany, with the option of studying for a joint degree award from both Universities.
Keywords: epididymis, vas deferens, activin-follistatin interaction

89. Investigation of the novel phenotype of testicular macrophages

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Mark Hedger

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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.
Keywords: macrophages, activin, testosterone

90. Investigation of activin regulation in inflammation and infertility caused by diabetes

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Mark Hedger

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Project Description: Diabetes mellitus and elevated blood glucose levels are associated with the formation of irreversible advanced glycation end structures and increased sperm damage. It is proposed that glycation adducts induce low-grade inflammation in the male reproductive tract, resulting in impairment of spermatogenesis. The inflammatory cytokine activin and its binding protein, follistatin, are implicated in regulating inflammation, spermatogenesis and diabetes, but have not been investigated specifically in regard to the loss of male fertility that accompanies diabetes. This project will investigate the role of activin and follistatin in inflammation and sperm damage in models of diabetes in mice. This is a collaborative research project that will involve 6-12 months research time at the Justus Liebig University in Giessen, Germany, with the option of studying for a joint degree award from both Universities.
Keywords: diabetes, infertility, sperm damage, activin, follistatin

91. Investigation of inflammation of the male reproductive tract and infertility

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Mark Hedger

Email: mark.hedger@hudson.org.au

Phone: 03 8572 2779

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 has both pro-inflammatory 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. Students undertaking this project at postgraduate level may also have the opportunity to undertake 6-12 months collaborative research at the Justus Liebig University in Giessen, Germany, with the option of studying for a joint degree award from both Universities.
Keywords: infertility, inflammation, fibrosis, activin, follistatin therapeutic intervention

RESEARCH GROUP: Embryo Implantation

92. Development of a new treatment strategy for endometrial cancer that preserves fertility

Theme: Women's, Children's and Reproductive Medicine

Suitability: Doctorate

Project Leader: A/Prof Eva Dimitriadis

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Phone: 03 8572 2546

Project Description: Endometrial cancer is the most common gynaecological malignancy. Advanced disease has a very poor prognosis and current treatment options for advanced disease are inadequate; thus novel treatments for recurrent disease are required. We have identified proteins and microRNA that may be important in disease progression and are determining the effect of targeting these proteins as novel treatments. We will use in vivo mouse models, in vitro models and clinical material for this project.
Keywords: endometrial cancer, treatments, fertility

93. Nanoparticles targeting the uterus and placenta: utility in developing targeted treatments for infertility and pregnancy disorders

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Doctorate

Project Leader: A/Prof Eva Dimitriadis

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Phone: 03 8572 2546

Project Description: The World Health Organisation has reported that infertility is the third-most severe disease worldwide. We have identified factors that may be targeted to treat infertility and pregnancy disorders, including pre-eclampsia and intrauterine growth restriction. This project will investigate specific targeting of the uterus and placenta to treat these disorders and whether potential off-target effects can be eliminated. The project will investigate sustained release of the agents using FDA-approved nanoparticles and nanofibres in vitro, using cell culture. In addition, it will investigate the use of nanoparticle delivery of agents to target the uterus to treat or prevent infertility and diseases associated with abnormal placentation such as pre-eclampsia.
Keywords: infertility, treatments, pre-eclampsia, placenta

94. Improving IVF outcomes by facilitating implantation

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Doctorate

Project Leader: A/Prof Eva Dimitriadis

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Project Description: We have identified epigenetic mechanisms by which human embryos may regulate their fate to implant. This project will investigate the effect of these factors on facilitating embryo development and implantation into the uterus. It will use innovative cell culture models and in vivo mouse models to determine the function of the epigenetic regulators we have identified. This work has the potential to be used as a treatment to facilitate implantation in women with implantation failure associated infertility.
Keywords: human embryos, IVF, infertility

RESEARCH GROUP: Implantation and Placental Development

95. Uterine surface transformation for embryo implantation and IVF success

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Guiying Nie

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Phone: 03 8572 2550

Project Description: The uterus acts as 'fertile soil' for the embryo to implant and grow. However, for implantation to succeed, the uterus must remodel substantially to become 'receptive', as the surface of the uterus is normally non-receptive to embryo attachment. Defective uterine receptivity is a major cause of implantation failure in IVF treatment; this is of particular concern, since IVF use is increasing yearly as more women choose to have children at a later age. We study the mechanisms governing uterine preparation for embryo implantation. This project will investigate a particular group of cell-surface proteins that change production and localisation during the establishment of uterine receptivity in women. It will use a number of approaches, including molecular biology and cell culture, to establish the functional importance of these proteins in uterine fertility and infertility, with a long-term goal of improving implantation rate in IVF treatment.
Keywords: embryo implantation, IVF, uterus, uterine receptivity, cell-surface remodelling

96. Post-translational regulation of uterine fertility/infertility and clinical implications

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Guiying Nie

Email: guiying.nie@hudson.org.au

Phone: 03 8572 2550

Project Description: The uterus requires substantial remodelling for implantation to occur. Proprotein convertases (PCs) are a family of 'master switch' serine proteases to post-translationally regulate numerous proteins of critical importance. We have identified that one of such proteases, PC6, is essential for making the uterus receptive for embryo implantation. To understand how PC6 regulates uterine receptivity, we used proteomics and identified a group of proteins that are tightly regulated by PC6. These newly identified PC6-regulated proteins have never been characterised in the uterus and their contribution to normal and abnormal uterine function is unknown. This project will establish the functional importance of these proteins in uterine receptivity, fertility and infertility. This project will also explore the clinical utility of PC6 and/or PC6-regulated proteins as potential biomarkers and treatment targets to improve IVF success.
Keywords: embryo implantation, uterine infertility, IVF, protease, post-translational regulation

97. Stress-related genes in pregnancy disease pre-eclampsia

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Master by Research, Doctorate

Project Leader: A/Prof Guiying Nie

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Phone: 03 8572 2550

Project Description: Pre-eclampsia is a life-threatening disorder of pregnancy, characterised by a sudden increase in blood pressure and urine protein after 20 weeks of gestation in previously normotensive women. Pre-eclampsia is a medical emergency, as it can progress to multi-organ disorder associated with renal failure, seizures and stroke. Currently the only effective 'cure' for pre-eclampsia is to terminate the pregnancy and deliver the baby, often prematurely. Although causes of pre-eclampsia are multi-factorial, it is well established that the placenta is sufficient and necessary to cause pre-eclampsia. It is also emerging that placental stress contributes to pre-eclampsia development. This project will investigate a number of stress-related factors in pre-eclampsia, with a long-term goal of developing early diagnosis and potential treatment for pre-eclampsia.
Keywords: pregnancy disorders, placenta, pre-eclampsia, diagnosis, treatment

RESEARCH GROUP: Male Fertility Regulation

98. Male germ cells and the blood-testis barrier

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Master by Research, Doctorate

Project Leaders: Dr Peter Stanton, Dr Liza O'Donnell

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Project Description: During spermatogenesis, early male germ cells (spermatocytes) cross the blood-testis barrier into a protected environment in order to complete their maturation. This migration step is critical for sperm output, but its regulation is poorly understood. We have found a new mechanism by which particular types of germ cells can directly regulate blood-testis barrier function, which includes the expression of novel tight junction proteins. This project will investigate this new mechanism, with aims to identify the factor(s) and tight junction proteins involved, and their relevance to male fertility. Methods include in vitro and in vivo models of blood-testis barrier function, qPCR, western blotting and confocal immunocytochemistry.
Keywords: testis, fertility, reproduction, cell-cell communication

99. How does activin regulate adult testis function?

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Master by Research, Doctorate

Project Leaders: Dr Peter Stanton, A/Prof Craig Harrison

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Phone: 03 8572 2689

Project Description: Mature, differentiated Sertoli cells are essential for spermatogenesis to occur in the adult. We recently found that activin A can cause Sertoli cells, which 'nurse' the developing germ cells, to revert to an immature de-differentiated phenotype, suggesting a novel role for activin in testicular disease. This project will use in vitro and in vivo models to determine the molecular mechanisms of activin action on mature Sertoli cell function.
Keywords: male reproduction, growth factors, cell-cell communication, fertility, spermatogenesis

100. Developing better tests and treatment for male infertility

Theme: Diabetes, Obesity, Men's Health and Endocrinology

Suitability: Honours, Doctorate

Project Leaders: Dr Peter Stanton, Prof Robert McLachlan

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Phone: 03 8572 2689

Project Description: Infertility affects 1 in 20 men, but in most cases there are no known molecular reasons why spermatogenesis has failed. We found that the fluid that surrounds testicular tubules where sperm are made contains numerous proteins that could be important in their production. Hence the aim of this project will be to use proteomics to identify protein markers useful for the prediction of male fertility. Methods include ELISA, SDS-PAGE, western blotting, immunohistochemistry, mass spectrometry and cell culture.
Keywords: infertility, spermatogenesis

RESEARCH GROUP: Brain and Gender

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

Theme: Neuroscience and Psychiatry

Suitability: Honours, Master by Research, Doctorate

Project Leader: Dr Joohyung Lee

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Phone: 03 8572 2507

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 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 neurosurgery, behavioural neuroscience, neuroanatomy, and cellular and biology techniques.
Keywords: brain sex differences, SRY, dopamine, neurodevelopmental disorders

102. De-masculinising the male brain

Theme: Neuroscience and Psychiatry

Suitability: Honours, Master by Research, Doctorate

Project Leader: Dr Joohyung Lee

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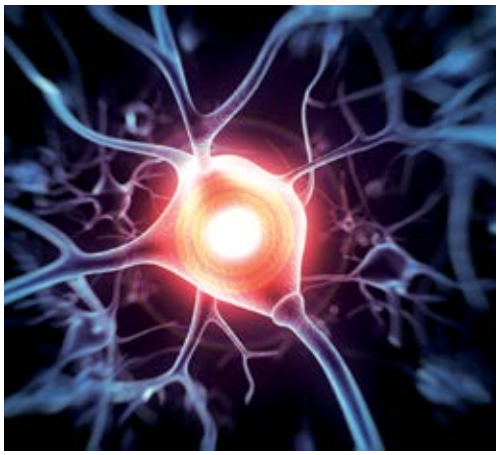
Phone: 03 8572 2507

Project Description: The Y-chromosome gene, SRY, is widely expressed in the male brain, in regions such as the substantia nigra, ventral tegmental area (VTA), prefrontal 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 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 (RNA seq, ChIPseq).
Keywords: brain sex differences, SRY, dopamine, neurological disorders



THE RITCHIE CENTRE

Centre Head: Professor Stuart Hooper

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

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.

The Centre has more than 160 research staff and students, including fetal physiologists, sleep physiologists, immunologists, stem cell biologists, neonatologists, paediatricians, obstetricians, gynaecologists and radiologists.

Research Themes:

Women's Health:

A/Prof Caroline Gargett

Fetal and Neonatal Health:
Respiratory and Cardiovascular:

Prof Stuart Hooper
A/Prof Tim Moss

Fetal and Neonatal Health:
Brain Injury and Neurodevelopment:

Prof David Walker
A/Prof Suzie Miller

Infant and Child Health:

Prof Rosemary Horne
A/Prof Jim Buttery

Cell Therapy and Regenerative Medicine:

Prof Graham Jenkin
Prof Euan Wallace

Research Theme: Women's Health

103. Testing the in vivo regenerative potential of putative stem cell populations from the endometrium

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: A/Prof Caroline Gargett, Dr James Deane

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Phone: 03 8572 2792 (Dr Deane)

Project Description: The endometrium is the lining of the uterus and contains adult stem cells that are thought to be responsible for its ability to rapidly regenerate during each menstrual cycle. Finding markers to identify endometrial stem cells is an important area of research. We are investigating candidate endometrial stem cells using cell surface markers in human tissue, and transgenic reporters in mice. The ultimate test of stem cell potential is whether these cells can form endometrium. To answer this question, we will assess the ability of putative endometrial stem cells from mouse and human to produce endometrium when transplanted into a mouse.
Keywords: endometrium, epithelial stem/progenitor cells, human, mouse, xenograft

104. Characterising the perivascular location of human endometrial mesenchymal stem cells

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: A/Prof Caroline Gargett, Dr James Deane

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Phone: 03 8572 2792 (Dr Deane)

Project Description: We discovered a small mesenchymal stem cell population in human endometrium (eMSC) likely responsible for its regeneration each month during the menstrual cycle. We also identified specific surface markers of eMSC: CD140b+CD146+ co-expression and SUSD2. Both markers show the perivascular location of eMSC. CD140b+CD146+ cells are pericytes closely

associated with endothelial cells, but the precise location of SUSD2+ eMSC is unknown. In a sheep model, we found that CD271+ eMSC were also perivascular, located in the adventitia of larger vessels rather than pericytes. SUSD2+ cells are shed during menstruation and enter the pelvic cavity in greater numbers in women with endometriosis compared to normal, likely contributing to its pathogenesis. This project will undertake a detailed analysis of human endometrium using sophisticated microscopy to determine the precise perivascular locations of eMSC. Co-localisation with other stem cell markers (OCT4, SOX2, NANOG) and oestrogen and progesterone receptors from normal and endometriosis women will also be examined. This project will generate beautiful images showing precisely where eMSC reside.
Keywords: endometrium, mesenchymal stem/stromal cells, endometriosis, blood vessels, confocal microscopy

105. Do endometrial mesenchymal stem cells (MSC) have immunomodulatory properties that can be harnessed to treat human disease?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr James Deane, A/Prof Caroline Gargett

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Phone: 03 8572 2792 (Dr Deane)

Project Description: Mesenchymal stem cells (MSC) are rare populations of undifferentiated cells found in many tissues that are capable of self-renewal and differentiating into multiple mesodermal lineages. We first discovered a new and easily accessible MSC population in the endometrium, the highly regenerative lining of the uterus (eMSC). MSC from other tissues such as bone marrow and fat have immunomodulatory properties, which makes them ideal for treating diseases involving over-exuberant or off-target immune responses, and also allows their use in non-identical individuals. We have shown that eMSC inhibit mouse immune cells in an in vitro setting. We are now seeking to demonstrate the clinical utility of eMSC by confirming that they can inhibit human immune cells in an in vitro setting, and investigating their ability to inhibit a complete in vivo immune response in mouse models of inflammation.
Keywords: endometrium, mesenchymal stem/stromal cells, immunomodulation, mouse model, human

106. Role of endometrial stem/progenitor cells in endometrial injury-induced doubling of pregnancy rates in IVF procedures

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leader: A/Prof Caroline Gargett

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Phone: 03 8572 2792 (Dr Deane)

Project Description: Recently it was discovered that an endometrial biopsy taken during the cycle before embryo transfer in in vitro fertilisation (IVF) procedures doubles the pregnancy rate. However, the reason for this is not known. This project will examine whether biopsy-induced tissue damage activates endometrial stem/progenitor cells, which produce an overabundance of new endometrial cells generating an endometrium thick enough to support pregnancy in subsequent cycles. Flow cytometry will be the method of analysis.
Keywords: endometrium, stem/progenitor cells, IVF, pregnancy rate, tissue damage

107. How are endometrial stem cells regulated?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr James Deane, A/Prof Caroline Gargett

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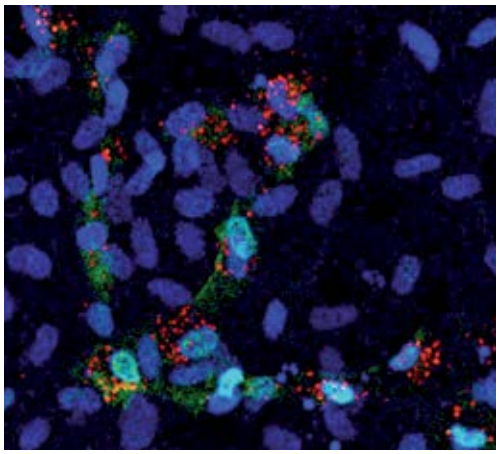
Phone: 03 8572 2792 (Dr Deane)

Project Description: Stem cells are believed to be responsible for the regenerative potential of the endometrium. We have used markers to identify putative endometrial stem/progenitor cells in the human and mouse uterus, but how the growth and differentiation of these cells is controlled is unclear. Hedgehog signalling is a developmental pathway that is modulated during endometrial regeneration and overactivated in endometrial cancer. We have evidence that Hedgehog signalling exerts its influence on endometrial growth by influencing stem/progenitor cells. This project will use cultured human endometrial stem/progenitor cells and mouse models of endometrial regeneration, using telomerase reporter mice to examine the role of Hedgehog signalling in regulating endometrial stem cells.
Keywords: endometrium, stem/progenitor cells, transgenic mouse models, Hedgehog signalling, regeneration



108. Telomerase activity as a stem cell marker in the endometrium

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr James Deane, Dr Fiona Cousins, A/Prof Caroline Gargett

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Phone: 03 8572 2792 (Dr Deane)

Project Description: Stem cells are believed to be responsible for the regenerative potential of the endometrium. Markers for mouse endometrial stem cells are required to study endometrial regeneration. To this end, we have investigated the endometrial activity of the telomerase complex, which allows stem cells to divide indefinitely by maintaining telomere length. We have used transgenic mice expressing telomerase reporter constructs to identify putative stem cells in the endometrium. This project will use telomerase reporter mice to study stem cells in normal endometrial cycling, endometrial shedding and repair (as in the human menstrual cycle), and endometrial repair and regeneration after pregnancy.
Keywords: endometrium, stem cell, telomerase

109. Ex vivo perfusion of the term human placenta - establishing a technique for measuring placental creatine transport

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Hayley Dickinson, Dr Padma Murthi, Dr Stacey Ellery, Prof Rod Snow

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Phone: 03 8572 2826 (Dr Dickinson)

Project Description: During pregnancy, the increasing nutrient demands of the placenta and fetus impose a considerable metabolic load on the mother. As such, many problems in pregnancy, such as poor fetal growth and stillbirth, develop due to cellular energy failure arising from inadequate nutrient and/or oxygen supply to the fetus. We have compelling evidence that creatine is a critical cellular energy metabolite for pregnancy and high creatine supply protects the fetus from compromise and death. In identifying the main sources of creatine during pregnancy, we recently discovered that the term human placenta synthesises creatine.
This project will establish the technique of dual placental perfusion to determine the rate of creatine transport across the placenta. This study will involve out-of-hours work, as it relies on delivery of human placentas, which can occur at any time (usually in the evening and the weekend). This project is recommended for a student who lives nearby and is willing to be flexible with time.

110. Uncovering mechanisms underlying ethnic disparities in maternal and perinatal outcomes

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Miranda Davies-Tuck, Dr Padma Murthi, Prof Euan Wallace

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Phone: 03 8572 2841

Project Description: Despite growing evidence for an association between ethnicity and adverse perinatal and obstetric outcomes, the possible mechanisms underlying the relationship(s) are unknown. Understanding why women of different ethnicities are at 'higher risk' of adverse maternal and perinatal outcomes is important. A range of projects is available using routinely collected or recorded pregnancy and birth data, as well as biological data from the mother and baby at the birth.

111. How does maternal vitamin D deficiency during pregnancy contribute to neurocognitive deficits in infants and children?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Padma Murthi, Prof Peter Ebeling

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Phone: 03 8572 2874

Project Description: Maternal vitamin D deficiency during pregnancy has been linked to impaired neurocognitive and language development in children. The mechanism by which vitamin D affects childhood neurocognitive outcomes is unclear, but may be via interactions between vitamin D and the serotonin pathway. Serotonin is an important neurotransmitter involved in fetal brain development. Vitamin D modulates serotonin synthesis. We hypothesise that vitamin D deficiency contributes to disruption in fetal serotonin signalling during pregnancy. We aim to understand the biological mechanism(s) by which vitamin D regulates fetal serotonin signalling pathways using human term placental tissues. We will define molecular pathways by which vitamin D regulates serotonin synthesis using molecular and protein analyses in placental cell cultures (in vitro) and in placental perfusion system (ex vivo).

112. How does vitamin D influence feto-placental growth?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Padma Murthi, Dr Hayley Dickinson, Dr Stacey Ellery, A/Prof David Walker

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Phone: 03 8572 2874

Project Description: Maternal vitamin D supplementation during pregnancy improves fetal growth. However, the mechanism by which vitamin D promotes fetal growth is largely unknown. We aim to identify the effect of different vitamin D analogues and their mechanism of action in promoting placental growth in first trimester and term placental tissues. We will also define how vitamin D analogues influence placental blood flow and nutrient transport systems across the maternal and fetal compartments in term pregnancies, using ex vivo placental perfusion system and in vitro placental cell cultures.

113. How does placental insufficiency affect nutrient transport?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Padma Murthi, Dr Hayley Dickinson, Dr Stacey Ellery, A/Prof David Walker

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Phone: 03 8572 2874

Project Description: Placental maldevelopment and function lead to poor fetal growth, preterm labour and increased neonatal morbidity. Placental insufficiency is often associated with pre-eclampsia, gestational diabetes and fetal growth restriction. The placenta plays a critical role both in the synthesis and transport of nutrients, including amino acids and micronutrients for the fetus. In this project, we will determine if placental insufficiency is associated with alterations of amino acids and vitamin D transporters and their binding proteins in pre-eclampsia, fetal growth restriction and gestational-diabetes pregnancies, using real-time PCR, immunoblotting and immunocytochemistry techniques.

114. Novel treatments for pre-eclampsia

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Bryan Leaw, Prof Euan Wallace

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Phone: 03 8572 2797 (Dr Leaw)

Project Description: Pre-eclampsia is a serious pregnancy-specific condition affecting approximately 5% of pregnancies worldwide. It is a leading cause of maternal and fetal morbidity and mortality. To date, there is no cure for pre-eclampsia. Resveratrol is becoming increasingly well known for its protective effects against cancer, cardiovascular disease, inflammation, obesity, age-related deteriorations and ischaemic injuries, such as myocardial infarctions and stroke. Its potential as a therapeutic for pre-eclampsia is yet to be investigated in detail. Using a rat model of pre-eclampsia, we will determine the therapeutic benefits of several new anti-oxidative compounds. This project involves small animal surgery and molecular techniques.

115. Placental pathology of births at Monash Health

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Hayley Dickinson, Dr Padma Murthi, Dr Miranda Davies-Tuck

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Phone: 03 8572 2826 (Dr Dickinson)

Project Description: Placentae are routinely sent for pathological assessment at Monash Health after an adverse pregnancy outcome such as preterm birth, fetal growth restriction, pre-eclampsia and stillbirth. This project will access these previously collected data, review the histology and clinical notes, and determine relationships between these and the available pregnancy data, maternal demographics and baby outcomes data. This study will describe the relationship between placental health and adverse pregnancy events at Monash Health.

Research Theme: Fetal and Neonatal Health

116. Supplementing the diet with creatine at the end of pregnancy: a possible treatment to prevent perinatal brain damage in preterm and term lambs?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof David Walker, A/Prof Suzie Miller, Dr Hayley Dickinson, Dr Graeme Polglase

Email: david.walker@monash.edu

Phone: (03) 8572 2823 (A/Prof Walker)

Project Description: The aetiology of brain damage that manifests itself in some infants after prolonged labour or hypoxic birth is still not understood. Current treatments such as head cooling, or use of noble gases such as xenon or argon are 'rescue' treatments with limited effectiveness. Our recent work in pregnant sheep and a precocial rodent shows that adding creatine to the maternal diet in the latter stages of pregnancy protects the fetal brain against the effects of severe hypoxia at birth. The aim of our on-going studies is to show that this creatine treatment improves the resuscitation and development of locomotor function in lambs delivered preterm or at term, with or without the additional challenge of birth hypoxia.

117. Establishing the placental phenotype in a spiny mouse model of reduced fetal growth

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Masters by Research

Project Leaders: Dr Hayley Dickinson, Dr Stacey Ellery, Dr Padma Murthi

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Phone: 03 8572 2826 (Dr Dickinson)

Project Description: Fetal growth restriction (FGR) is a major obstetric problem, contributing to neonatal morbidity and mortality. FGR continues to present problems due to difficulty of antenatal detection and no effective preventative or interventional strategy. We have developed a model of FGR in the spiny mouse by restricting uterine blood flow for the last 25% of gestation. Once validated and characterised, we will use this model to test preventative and interventional strategies to improve outcomes for the fetus. This project will describe the structure and molecular profile of the term placenta from this model.

118. Brain creatine levels in preterm infants

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Hayley Dickinson, A/Prof Flora Wong, A/Prof Michael Fahey, A/Prof David Walker, Prof Rod Snow

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Phone: 03 8572 2826 (Dr Dickinson)

Project Description: Preterm birth is associated with long-term neurological deficits and currently no effective treatment exists to lessen these burdens. We have discovered that creatine is produced in large amounts by the human placenta, implying an importance to the developing fetus, and our animal studies demonstrate that fetal creatine synthesis develops only very late in gestation (0.9 in a precocial rodent species). In this context, preterm birth has the effect of removing the fetus (premature neonate) from the protective environment where the mother and placenta supply creatine to it. The very low level of creatine in breast milk, formula milk and parenteral nutrition cannot prevent the possibility that preterm infants become creatine deficient, with detrimental effects on brain function and development. The known syndromes of cerebral creatine deficiency are associated with significant neurological impairment of the neonate and child, including mental retardation, expressive speech and language delay, autism-like behaviour and epilepsy. These conditions are frequently misdiagnosed as cerebral palsy. We propose to determine plasma and urine creatine concentrations in preterm and term infants throughout the duration of their hospital stay, and to measure brain creatine content using MRI.

119. Assessing behaviour in spiny mouse offspring: effects of birth asphyxia and effectiveness of creatine to prevent injury

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, Masters by Research

Project Leaders: Dr Hayley Dickinson, Dr Stacey Ellery, A/Prof David Walker

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Phone: 03 8572 2826 (Dr Dickinson)

Project Description: Over the past 8 years, we have developed and validated a model of birth asphyxia in the spiny mouse that mimics many features of the clinical condition hypoxic-ischemic encephalopathy (HIE). This project will analyse, interpret and visualise behavioural data collected from a large cohort study performed by previous PhD students in our laboratory. This project will determine whether behaviour is altered in offspring exposed to birth asphyxia and whether maternal dietary creatine supplementation is protective, as we have shown it is for brain structure, kidney structure and function, and muscle structure and function.

120. Impact of dopamine in the immature brain

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Flora Wong, A/Prof David Walker, A/Prof Suzie Miller

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Phone: 03 9594 5482 (A/Prof Wong)

Project Description: Dopamine is commonly prescribed to preterm babies to raise their blood pressure, but its effect in the immature brain is uncertain. New data suggest that dopamine may improve brain oxygenation. This project aims to define the effects of dopamine in the immature brain using a preterm lamb model, to evaluate the therapeutic potential of dopamine in improving brain oxygenation and reducing brain injury in preterm babies. In preterm lambs receiving dopamine, we will correlate changes in blood pressure, cerebral blood flow and metabolism with histopathology in brain slides, in order to assess the effect of dopamine in reducing brain injury.

121. Coupling between brain activity and brain blood flow in the immature brain

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Flora Wong, A/Prof David Walker

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Project Description: Increase in brain activity is normally matched by an increase in brain blood flow to meet the metabolic demand. This is known as neurovascular coupling, which is an important function in adults. However, little is known about neurovascular coupling in newborn babies. We aim to examine neurovascular coupling in the immature brain. In newborn lambs, we will measure changes in brain activity and brain blood flow. We will perform the studies in the Australian Synchrotron for state-of-the-art imaging of the brain blood vessels. We will also assess how different drugs used on sick human babies would affect the immature brain.

122. Are sick preterm infants sleeping in prone position at risk of low brain oxygen levels?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

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

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Project Description: It is common practice for sick, preterm babies receiving intensive care to sleep on both their front (prone) and back (supine) alternately while in hospital. However, our recent study shows that healthy term babies sleeping prone have lower brain oxygen levels. Preterm babies receiving intensive care are particularly vulnerable to brain injury due to low brain oxygen levels. We therefore aim to determine whether the current practice of prone sleeping in sick babies is compromising the developing brains of these vulnerable infants, by measuring brain oxygen at the babies' bedside with a spectrometer (near infrared spectroscopy).

123. Use of activated protein C (aPC) to reduce brain injury from birth asphyxia

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Flora Wong, A/Prof David Walker, Dr Hayley Dickinson

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Project Description: Birth asphyxia leads to significant brain injury and long-term neurodevelopmental problems, including cerebral palsy, cognitive and other neurological dysfunction. Activated protein C (aPC) is a vitamin-K-dependent plasma glycoprotein, and has been shown to be neuroprotective in adult animal models of brain injury and stroke. We propose to explore aPC as a possible new therapy for brain injury following birth asphyxia. We will use our well-validated model of birth asphyxia in the spiny mouse to determine if treatment of birth-asphyxiated pups with aPC prevents the neuropathology in brain slides, and improves postnatal behavioural deficits.

124. Ganaxolone: a new treatment for neonatal seizures

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Tamara Yawno, A/Prof Suzie Miller, Dr Michael Fahey, A/Prof David Walker

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Project Description: Seizures in neonates are relatively common; they are powerful predictors of long-term cognitive and developmental impairment. There is also a significant concern about current anti-seizure therapies, which can cause brain injury as they have the potential to be neurotoxic. We will investigate the effects of the synthetic GABAA agonist ganaxolone, or phenobarbitone given at the onset of seizure caused by hypoxia ischaemia in term fetal sheep. This project will utilise our established fetal sheep model, with state-of-the-art monitoring equipment to investigate brain activity and brain histopathology. Keywords: ganaxolone, neonatal seizures, brain injury, newborn, brain activity

125. Sildenafil treatment in growth-restricted fetuses: what are the effects on brain structure

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Beth Allison, A/Prof Suzie Miller, Dr Graeme Polglase

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Project Description: Intrauterine growth restriction complicates 8% of pregnancies and increases risk for preterm birth and adverse brain development. Although there is no cure, sildenafil citrate (Viagra) is currently being trialed during human pregnancy. Sildenafil is thought to increase the blood flow through the placenta and increase nutrient and oxygen delivery to the developing baby. Despite its promise for growth-restricted babies, sildenafil may also have effects in the fetus as it crosses the placenta. This project will be undertaken in pregnant sheep exposed to sildenafil and use techniques such as histology, inflammatory assays, RT-PCR and western blotting to investigate brain structure following exposure to sildenafil.

126. The effects of betamethasone in single and repeat doses on the developing brain

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Suzie Miller, Dr Tamara Yawno, Prof Graham Jenkin

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Project Description: Betamethasone is routinely administered to pregnant women in preterm labour to mature the fetal lungs and aid preterm survival of the neonate. In this regard, betamethasone is accepted as a life-saving treatment. However, betamethasone has other non-pulmonary effects, particularly on the cardiovascular system and brain. We will administer betamethasone in single or repeat doses to pregnant sheep carrying either a well-grown or intrauterine growth-restricted (IUGR) fetus and examine cerebral physiological and cellular responses, to correlate with neuropathology. We hypothesise that brain growth and development will be adversely affected in IUGR fetuses, particularly with repeat betamethasone. Neuroprotective options for IUGR fetuses will be considered.

127. Exploring a new frontier: the immune and coagulation systems of the premature infant and their relevance for the risk of the major diseases of prematurity

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: A/Prof Marcel Nold, Dr Claudia Nold

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Phone: 03 8572 2776 (A/Prof Nold), 03 8572 2775 (Dr Nold)

Project Description: Direct clinical relevance: high. Hands-on learning opportunities: multi-colour flow cytometry, protein arrays, cell culture of primary human blood cells.
The immune and coagulation systems of preterm infants are largely unknown, a problematic blank page for clinicians, a true frontier for researchers. The dearth of information on preterm immunity and coagulation is explained by our inability until recent times to extract large amounts of information from the 0.5 ml samples available from the tiny patients, remembering they have as little as 35 ml of blood. Our laboratory is conducting an exciting study on blood taken from extremely premature infants at five time points, thus allowing for a unique longitudinal view of plasmatic and cellular immunity as well as coagulation. To explore these systems in depth, we use cutting-edge methods such as protein arrays and multi-colour flow cytometry, which students will learn. Access to the babies' clinical data enables us to perform correlation analyses to probe the relevance of our findings to the major diseases of prematurity, such as bronchopulmonary dysplasia, intracranial haemorrhage and necrotising enterocolitis. These insights may identify biomarkers and/or new therapeutic targets, which are direly needed as several of these diseases are life-threatening and currently untreatable.

128. Molecular tracking of the cytokine interleukin-37 in anti-inflammatory signalling

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, PhD

Project Leaders: A/Prof Marcel Nold, Dr Claudia Nold, Dr Kirstin Elgass, Dr Devi Ngo

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Project Description: Direct clinical relevance: medium/low. Hands-on learning opportunities: confocal microscopy, molecular engineering (cloning), cell culture of primary human blood cells and cell lines.
Many of the major diseases of prematurity, and of old age, are typified by an intense and run-away inflammation. In this program, we plan to elucidate the molecular signalling cascades triggered by what is perhaps the most powerful anti-inflammatory cytokine so far discovered, interleukin 37 (IL-37). The two leaders of the Nold laboratory were central figures in discovering the anti-inflammatory actions of IL-37 in 2010. Over the past 5 years, we have discovered the receptor through which Il-37 operates and we have been systematically laying the foundations for developing new and much-needed anti-inflammatory drugs based on IL-37. Our work recently identified the molecular features that endow IL-37 with its powerful beneficial effects, and in this program we will extend that understanding to exploit its therapeutic potential. This project continues our approach of utilising sophisticated high-resolution microscopy and live-cell imaging techniques to observe and track IL-37 and its signalling cascades in real time. Students will have the opportunity to learn and use methods involving tissue/cell culture, molecular engineering and micrometre-scale resolution imaging, as well as statistical analysis of the results.

129. Novel anti-inflammatory approaches for currently untreatable diseases of the preterm baby: IL-1Ra and IL-37 in animal models of bronchopulmonary dysplasia and necrotising enterocolitis

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, BMedSci

Project Leaders: Dr Claudia Nold, A/Prof Marcel Nold, A/Prof Philip Berger

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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, synchrotron X-ray imaging.

The severe chronic lung disease bronchopulmonary dysplasia (BPD) causes considerable suffering for premature infants and their families, and contributes substantially to healthcare 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 two innovative anti-inflammatory mediators, interleukin 1 receptor antagonist (IL-1Ra) and interleukin 37 (IL-37), protect against BPD and NEC. In newborn mice with a BPD-like lung disease, we will quantify whether increased levels of IL-1Ra or IL-37 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 for 3 days and brief exposure to cold and hypoxia, we will assess the protective properties of IL-1Ra.

130. Molecular characterisation of regulation and mechanism of action of the anti-inflammatory cytokine interleukin 37

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, BMedSci, PhD

Project Leaders: Dr Claudia Nold, Dr Ina Rudloff, A/Prof Marcel Nold

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Project Description: Direct clinical relevance: medium/low. Hands-on learning opportunities: culture of primary human blood cells and cell lines, protein detection by ELISA, RNA detection by real-time PCR, flow cytometry, immunohistochemistry. Interleukin (IL)-37 was discovered in silico in 2000, but it remained a neglected molecule, and nothing at all was known about its function until 2010, when we described the powerful anti-inflammatory properties of this cytokine. IL-37 belongs to the IL-1 family of cytokines and imparts a strong inhibition of the production of pro-inflammatory cytokines. Interestingly, this protection from inflammatory responses is not limited to one or a few triggers, but covers a wide spectrum of inflammatory assaults – a rare property, which renders IL-37 a prime candidate for clinical use. However, further research on the mechanism of action of this unusual cytokine is required before such steps can be taken. In this project, we will characterise several aspects of regulation and function of IL-37, in particular the mRNA and protein expression profile of IL-37 across a spectrum of cell types and the effect of IL-37 on one of the key molecular regulators of inflammation, the inflammasome.

131. The first in vivo exploration of interleukin-38

Theme: Infectious and Inflammatory Diseases

Suitability: Honours, BMedSci, PhD

Project Leaders: Dr Claudia Nold, Dr Ina Rudloff, A/Prof Marcel Nold

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Project Description: Direct clinical relevance: medium. Hands-on learning opportunities: various aspects of work with mice and patient samples, workup of tissues for various downstream applications, flow cytometry, histology, immunohistochemistry, protein detection by ELISA, RNA detection by real-time PCR. Interleukin (IL)-38 is a novel member of the IL-1 family of cytokines. The majority of IL-1 family members play important roles in inflammatory diseases – either as promoters or inhibitors of inflammation. IL-38, however, received almost no research attention until our group renamed the new IL-1 family cytokines in 2010. Thus, its function is still largely unknown. Recently, we discovered that IL-38 plays a role in systemic lupus erythematosus (SLE) – a very severe and potentially fatal autoimmune disease that mainly affects young women of childbearing age. We found that SLE patients have elevated serum IL-38 concentrations and that IL-38 is predictive of disease severity and the development of major SLE-associated complications. Moreover, we have shown in vitro that IL-38 has anti-inflammatory properties and inhibits the production of cytokines that promote inflammation.

Now, we want to investigate the function of IL-38 in vivo. For this purpose, we have generated the very first IL-38 knockout mouse that is not available anywhere else in the world. In this exciting project, we will undertake the first experiments using this mouse in a murine model of SLE, but will also perform experiments on blood samples directly obtained from SLE patients. Applying techniques such as ELISA, flow cytometry, real-time PCR and histology, we will aim to identify the role of IL-38 in SLE and potentially lay the foundation for a novel therapeutic approach for the treatment of SLE.

132. Transition to life after birth

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Stuart Hooper, Dr Kelly Crossley, Dr Graeme Polglase, Dr Lauren Kerr

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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 bypass the lungs during fetal life. Most infants smoothly make this transition, but many do not, which can be life threatening and cause lifelong 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.

133. Imaging the entry of air into the lungs at birth

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Stuart Hooper, Dr Lauren Kerr, Dr Marcus Kitchen (Physics)

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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.

134. Interrogating the nitric oxide pathway in the growth-restricted fetus?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr Beth Allison, A/Prof Suzie Miller, Dr Graeme Polglase

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Project Description: Cardiovascular disease is one of the leading killers in the developed world. It is well accepted that offspring of a sub-optimal pregnancy have an increased susceptibility to cardiovascular disease as they age. One of the leading causes of a sub-optimal pregnancy is fetal hypoxia leading to oxidative stress. It is because of this that nitric oxide pathways are thought to be involved. Despite this, little is understood about the role of the nitric oxide pathway during chronic fetal hypoxia, and therefore this will become the aim of this current project. This project will be using an array of techniques, including in vitro wire myography, real-time PCR, histology, immunohistochemistry and image analysis.

135. Preventing lung disease in very premature babies

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Megan Wallace, Prof Stuart Hooper

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Project Description: Very premature babies are born with immature lungs, so they often need respiratory support. However, this can injure their lungs and lead to abnormal lung development called bronchopulmonary dysplasia (BPD). There are no treatments to prevent or reverse BPD, because the mechanisms leading from injury to abnormal lung development are not known. We have recently identified several factors that are activated by injury and that may lead to BPD, suggesting they could be future therapeutic targets to prevent BPD. Several projects are possible to prove the involvement of these factors and could involve studies in premature rabbits and/or cell culture, together with molecular biology and immunohistochemical approaches.

136. Fetal lung growth and development

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Megan Wallace, Dr Annie McDougall

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Project Description: At birth the lungs must take on the role of gas exchange, a role they have never performed before. To survive, the lungs must be appropriately grown and mature by the time of birth. Babies born prematurely, before the lungs have had time to develop, are at high risk of death or disease. To improve the outcome for these babies, we must understand the mechanisms that regulate normal lung development, so that we can find new ways to accelerate it. This project will investigate factors that are likely candidates for mediating lung growth using cell culture and molecular biology approaches.

137. The role of Trop2 in trophoblast invasion, placental development and pre-eclampsia

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leader: Dr Megan Wallace, A/Prof Evdokia Dimitriadis, Dr Annie McDougall

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Project Description: During placental development, trophoblasts from the developing embryo invade into the maternal uterine lining, aiding placental development and remodelling the maternal spiral arteries to increase blood flow and nutrient supply to the developing fetus. Pre-eclampsia is a disease of pregnancy that is associated with poor trophoblast invasion and inadequate remodelling of the spiral arteries; this leads to maternal systemic endothelial cell dysfunction, hypertension and proteinuria. If untreated, pre-eclampsia can cause seizures and maternal death. The only treatment is to deliver the placenta and therefore the fetus, which places the newborn infant at increased risk of death or developing diseases of prematurity. Trop2 is a protein that was originally identified in trophoblasts, but its role in trophoblast cells is not known. In other cell types, Trop2 regulates cell proliferation, migration and invasion, and our pilot data suggest that its levels in the placenta are altered in pre-eclampsia. We hypothesise that Trop2 regulates trophoblast cell proliferation and invasion, and that it is important for placental development. We also hypothesise that low Trop2 levels will be associated with abnormal placentation, which contributes to the development of pre-eclampsia. This project will

involve the manipulation of Trop2 levels using small-interfering RNA to decrease Trop2 levels and overexpression vectors to increase Trop2 levels, in cultured human trophoblast cell lines, to assess the role of Trop2 in trophoblast proliferation and invasion. It will also involve the assessment of placental development in Trop2 knockout mice using histological techniques. If time permits, Trop2 levels will also be assessed in placentas from women with pre-eclampsia and from gestational-age-matched placentas.

138. Characterising the role of Trop2 in fetal development

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr Megan Wallace, Dr Annie McDougall, Dr Mary Tolcos

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Project Description: Trop2 is a protein that regulates cell proliferation and migration in tumours. Cell proliferation and migration are also features critical for fetal development. We have shown that Trop2 is highly expressed in most fetal organs and that it regulates cell proliferation and migration in the developing lung and brain. The aim of this project is to determine if Trop2 also regulates cell proliferation and migration in other fetal organs, by analysing fetal and neonatal organ development in Trop2 knockout mice. Students will be able to select their organ of interest for this project. The project will combine small animal work, histology, immunohistochemistry and molecular biology to characterise the role of Trop2 in organ development.

139. Amniotic fluid infection/ inflammation: effects on brain development and postnatal behaviour

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Tim Moss, Dr Hayley Dickinson, A/Prof David Walker

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Phone: 03 8572 2821 (A/Prof Moss)

Project description: Evidence of infection or inflammation within the uterus during pregnancy increases the risk of neurodevelopmental disorders like autism and cerebral palsy. The spiny mouse (Acomys cahirinus) is particularly suitable as a model of human pregnancy, and postnatal outcomes can be assessed using a battery of neurobehavioural tests.
This project is aimed at identifying the effects of experimental amniotic fluid infection (using ureaplasmas, the microorganisms most commonly identified in amniotic fluid of women who deliver preterm) on brain development and postnatal behaviour in spiny mice.
Research techniques: small animal experimentation (surgery, tissue collection, biometry); small animal neurobehavioural tests; histology; immunohistochemistry; molecular biology (RT-PCR); microbiology.

140. Gestation-dependent effects of virus-like illnesses in fetal brain development in the spiny mouse

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof David Walker

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Project description: Rodent models of maternal infection during pregnancy (also known as maternal immune activation [MIA]) reproduce many behavioural, cognitive and neurochemical changes in the offspring that signify major changes in brain development have occurred. The current epidemic of 'microcephaly' in Brazilian women infected with the Zika virus has lent urgency to understanding how viral infections affect brain development during pregnancy. We now want to see if a virus-like illness induced in early, mid or late pregnancy affects fetal brain development. Specifically, we want to determine the effects of Poly I:C treatment on development of the cerebral cortex in the spiny mouse fetus, to see if there is evidence of microcephaly at the end of pregnancy in this animal model.

141. Maternal immunisation against whooping cough: effect on brain development and postnatal behaviour

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Tim Moss, Dr Hayley Dickinson

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Project description: Development of immunity to whooping cough by immunising babies after birth leaves them vulnerable to infection in early life. Immunisation of the mother during pregnancy allows development of immunity in the fetus, thus providing protection from birth. However, activation of the maternal immune system during pregnancy can influence brain development and postnatal behaviour, and may lead to disorders such as autism and schizophrenia; whether maternal immunisation has this effect is unknown.
This project is aimed at assessing the effects on brain development and postnatal behaviour in spiny mice, after maternal immunisation against whooping cough.
Research techniques: small animal experimentation (injection, tissue collection, biometry); small animal neurobehavioural tests; histology; immunohistochemistry; molecular biology (RT-PCR).

142 Early life inflammation and cardiovascular disease

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Tim Moss, Prof David Burgner (MCRI)

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Project description: Atherosclerosis, a major cause of cardiovascular disease, is an inflammatory condition that has its origins in early life. Atherosclerosis develops for decades before becoming clinically apparent. Early life is therefore a potential but largely overlooked window of opportunity for interventions to prevent or slow the development of atherosclerosis. The early life determinants of the initiation and progression of atherosclerosis are poorly understood. Animal and human data clearly indicate that postnatal inflammation and infection accelerate the development of atherosclerosis and are associated with adverse clinical outcomes.

The aim of this project is to determine the effect of inflammation before and soon after birth on the development of atherosclerosis in mice predisposed to development of the disease.
Research techniques: small animal experimentation (surgery, injection, tissue collection, biometry); histology; immunohistochemistry; molecular biology (RT-PCR).

143. Improving the transition at birth in asphyxiated infants

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Graeme Polglase, Prof Stuart Hooper

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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.

144. Protecting the brain from injury at preterm delivery

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Graeme Polglase, Dr Kelly Crossley

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Project Description:
Brain injury is common in preterm infants and is a major cause of long-term adverse neurodevelopment, including mental disability and cerebral palsy. Human data and animal studies have shown that brain injury pertaining to preterm birth occurs through two major mechanisms: 1) an inflammatory cascade in the brain; and 2) alterations to cerebral blood flow. Our current research is focused on understanding how events that occur in utero, during the time of birth and upon subsequent respiratory support after birth, can lead to brain injury in preterm neonates. Several projects will focus on establishing techniques to reduce/prevent brain injury related to perinatal events. The experiments include whole-animal physiology, molecular biology and immunohistochemistry.

145. Tracking the movement of creatine between maternal and fetal compartments in sheep using stable isotopes

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof David Walker, Dr Hayley Dickinson, Prof Rod Snow (Deakin University)

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Project Description:
Our recent studies using creatine infused into either the maternal or fetal circulations provided no evidence for transplacental passage of creatine. However, the sheep placenta and chorioamniotic membranes are richly endowed with the creatine transporter protein, CrT1. Possible explanations are: (1) the CrT1 transporter is fully saturated at normal creatine concentrations found in maternal plasma; or (2) placental CrT1 functions to distribute creatine between the placenta and fetus. We will use a stable isotope of creatine (13C-methyl-creatine) to: (i) measure the rate of isotope transfer across the placenta in pregnant sheep near term; (ii) use ex vivo methods to determine isotope uptake by placental samples; and (iii) transfer isotopic creatine across isolated segments of chorion/amnion using an Ussing chamber.

146. Effect of maternal asthma on fetal/neonatal lung development and function

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Rob Bischof, A/Prof Tim Moss, Dr Megan Wallace

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Project Description: Asthma is a common chronic disease affecting pregnant women and is a well-known risk factor for adverse outcomes in mother and baby. This project aims to investigate the effects of maternal asthma on fetal lung development and neonatal lung function in sheep, and identify mechanisms responsible for increased risk of neonatal lung disease. The outcomes of corticosteroid use in maternal asthma and in antenatal care on fetal/neonatal lung development and function will also be examined. The project will involve live animal studies, immunology, and cell and molecular biology.

147. Identifying the impact of viral illness in pregnancy on the fetal brain using the spiny mouse

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof David Walker, Dr Rachel Hill

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Project Description: Schizophrenia is a severely debilitating neuropsychiatric disorder that affects approximately 1% of the population. Epidemiological data identify maternal infection (i.e. activation of the immune system) during pregnancy as a strong aetiological risk factor for schizophrenia. Rodent models of maternal immune activation (MIA) produce many of the behavioural, cognitive and neurochemical features of schizophrenia in the offspring, and so provide highly tractable tools for testing new therapeutic approaches. Our goal is to explore potential preventative strategies that can be implemented antenatally in the event of maternal infection, before critical disruptions to brain development have taken place. This behavioural neuroscience project will determine whether antenatal treatments based on preventing MIA after induction of a maternal viral-like illness will prevent behavioural dysfunctions that otherwise occur in the adult offspring.

Research Theme: Infant and Child Health

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

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

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

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Project Description: Obstructive sleep apnoea (OSA) affects 1-3% of children and is a major health issue in childhood, with significant impacts on cognition, behaviour and cardiovascular health. The cardinal symptom of OSA is snoring. Approximately 35% of children snore - over one million children in Australia - but only about 10% of snoring children (1-3% of the population) will have OSA. Formally defining the presence of OSA in a snoring child requires polysomnography, a technically challenging and expensive (about $1000 each) test only available in paediatric tertiary referral hospitals. Such facilities could never meet the demand if all snoring children were referred. We are finalising development of a clinical scoring tool that will help predict children at highest risk of OSA without the need for polysomnography. In 2017 we will be testing the new tool for usability and accuracy. Is it helpful for GPs, ENT surgeons and paediatricians at the coal face?

149. The effects of preterm birth on the development and consequences of obstructive sleep apnoea in childhood

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Rosemary Horne, A/Prof Gillian Nixon, Dr Lisa Walter

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Project Description: Children born preterm are 3-5 times more likely to be diagnosed with obstructive sleep apnoea (OSA) than those born at term. We have previously shown in children born at term that OSA has significant effects on the cardiovascular system, with increased blood pressure and impaired autonomic control of heart rate. In our studies of infants born preterm, we have shown that they have impaired control of blood pressure and heart rate, which continues for at least the first 6 months after term equivalent age, but to date we have not carried out longitudinal studies into childhood. In this study, we will analyse overnight polysomnographic studies of children referred to the Melbourne Children's Sleep Centre, to identify if the severity and consequences of OSA are exacerbated in those children who were born preterm. Students will learn how to set up and record polysomnographic studies and to use spectral analysis techniques to assess heart rate control and cardiovascular responses to respiratory events.

150. Obstructive sleep apnoea in children with Down syndrome

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

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

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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 non-verbal 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.

151. Mobile phone video clips to aid diagnosis of obstructive sleep apnoea in children

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: A/Prof Margot Davey, A/Prof Gillian Nixon, Prof Rosemary Horne

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Project Description: When parents attend a paediatric sleep clinic outpatient appointment for assessment of their child's suspected obstructive sleep apnoea (OSA), they often bring a short video recorded on their mobile phone that they have taken at home of their child sleeping, to demonstrate the problem to their doctor. Currently, the diagnosis of OSA is achieved by performing overnight polysomnography (PSG), which is time-consuming and costly, and has limited availability nationwide. A previous study has used prolonged VHS video recordings to predict the presence or severity of OSA diagnosed on PSG. In this study, we will ask parents to record a video clip of their child during sleep according to specific instructions, and to send the recording to a designated email address. The video clips will be scored in a standardised fashion using a scoring sheet. PSG will then be performed as per usual clinical procedure. The relative risk of OSA given an abnormal video score will then be determined. If we can validate the use of home videos for predicting patients with OSA, then this tool could be used as a screening tool to prioritise clinic appointments, rationalise the use of further investigations and plan treatment.

152. Bright light therapy to improve sleep and quality of life in children with cancer

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Lisa Walter, Prof Rosemary Horne

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Phone: 8572 2834 (Dr Walter)

Project Description: Childhood cancer can disrupt sleep through the direct effect of the disease and/or a consequence of treatment. Poor sleep in children with cancer impacts on their perception of, and the ability to cope with, the emotional and physical challenges associated with both the disease and its treatment. Sleep disruption in these children is an added burden on their quality of life that can last many years beyond diagnosis and treatment. Bright light therapy has been shown to improve sleep and the quality of life in adults with cancer. A similar study has not been conducted in children. This study will investigate the efficacy of using bright light therapy in children with acute lymphoblastic leukaemia during chemotherapy, utilising actigraphy and validated questionnaires, to improve sleep and the quality of life of these children.

153. Are sleep spindles associated with neurocognitive deficits in children with sleep disordered breathing?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr Lisa Walter, Prof Rosemary Horne

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Phone: 8572 2834 (Dr Walter)

Project Description: A particular phenomenon of the electroencephalography (EEG) wave form is the sleep spindle, believed to function as a mechanism through which long-term changes are made in the neocortex and as a mechanism for maintaining sleep. Sleep spindles have also been associated with different aspects of cognitive performance in healthy children. Sleep disordered breathing (SDB) is a very common condition in children, and has been associated with neurocognitive deficits. To date, it is not known whether the poor neurocognition in children with SDB is related to a loss of sleep spindles. This study will investigate sleep spindles in children with SDB and determine if there is an association between sleep spindle numbers and neurocognitive deficits. The student will be involved in conducting sleep studies (polysomnography) and analysis of electroencephalography data.

154. Identifying pathways for new treatment strategies for children with primary snoring

Theme: Women's, Children's and Reproductive Medicine

Suitability: PhD

Project Leaders: Dr Sarah Biggs, Prof Rosemary Horne

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Phone: 03 8572 2835 (Dr Biggs)

Project Description: Children with primary snoring (PS) represent the greatest proportion of children with sleep disordered breathing (SDB) and are often untreated, leaving them at risk of continued or even increasing cognitive and behavioural deficit. An understanding of the mechanisms of the association between behaviour and learning will provide vital information regarding potential new, non-surgical treatment strategies. The aim of this project is to, for the first time, separate out the behavioural influence on cognitive potential in children with PS by examining the independent effect of SDB-related sleep disturbance on learning ability. This study will also provide novel data that may identify sleep-related brain activity as an underlying mechanism linking SDB with daytime neurocognitive and behavioural deficits in children with PS and obstructive sleep apnoea.

155. Preterm infants in the NICU – mechanisms of oxygen desaturations

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Kenneth Tan, Dr Atul Malhotra, A/Prof Philip Berger

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Phone: 03 9594 5191 (Dr Tan), 03 95945191 (Dr Malhotra), 03 9594 5398 (A/Prof Berger)

Project Description: A number of factors render preterm infants susceptible to hypoxaemic events, including low lung oxygen stores, high metabolic rate and a strong tendency for apnoeas to recur, with brief periods of intervening breathing (e.g. periodic breathing). Management is by increased oxygen therapy, which involves a strategy of adjusting inspired oxygen to maintain SpO2 within a target range based on pulse oximetry (oxygen saturation targeting). This may lead to secondary hyperoxia, as manual adjustment of oxygen often overshoots what is required. There is evidence that these episodes (of hypoxia and hyperoxia) contribute to adverse outcomes such as retinopathy of prematurity, bronchopulmonary dysplasia and poorer long-term neurodevelopment. The aim of this study is to study hypoxia/hyperoxia events in preterm infants in the NICU and methods for improving delivery of oxygen, including the role of automated oxygen delivery for preterm infants. This project will involve physiological measurements of infants receiving respiratory support (ventilation or CPAP) in the NICU, both from the ventilators and from additional research equipment.
The student will be conducting physiological measurements from infants in the NICU. This is part of the group's work on automated oxygen delivery to preterm infants.

156. SYNTRACK: linking emergency department data to detect outbreaks and vaccine safety signals

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, BMedSci, PhD

Project Leaders: A/Prof Jim Buttery, A/Prof Franz Babl, Dr Simon Craig

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Phone: 0403854179 (A/Prof Buttery)

Project Description: Direct clinical relevance: medium/high.
Hands-on learning opportunities: clinical emergency datasets, real-time extraction and upload programming, geocoding, signal detection methodologies.
De-identified real-time surveillance systems operating from emergency department (ED) diagnostic coding have been effective in the early detection of influenza outbreaks and biological threats. This project will establish the feasibility of linking three Melbourne paediatric EDs to map in time and place syndromes consistent with epidemic infectious diseases and vaccine safety signals. This pilot BMedSci project could be expanded nationally using the PREDICT paediatric ED network as an 'early warning' surveillance system for epidemic infectious diseases and vaccine safety signal in children.

157. SNOTWATCH: real-time seasonal viral information for health providers

Theme: Women's, Children's and Reproductive Medicine

Suitability: BMedSci

Project Leaders: A/Prof Jim Buttery, Dr Andrew Daley

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Phone: 0403 854 179 (A/Prof Buttery)

Project Description: Direct clinical relevance: medium/high.
Hands-on learning opportunities: hospital microbiology datasets, real-time extraction and upload programming, geocoding, signal detection methodologies.
This project will develop an automated real-time presentation of respiratory and gastrointestinal viral detections from hospital and community pathology providers to help clinicians determine the probability of what is causing common illness syndromes in children presenting to them. The information would be uploaded and presented on a publicly available website and weekly updates provided to GPs and emergency departments. The geotemporal data will be examined to determine evidence of predictable statewide spread of seasonal epidemic viruses.

158. Vaccine safety in general practice: can representation rates be used as an early warning surrogate for adverse event rates?

Theme: Women's, Children's and Reproductive Medicine

Suitability: BMedSci

Project Leaders: A/Prof Jim Buttery, Dr Nigel Crawford, Dr Jock Lawrie, A/Prof Chris Pearce

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Phone: 0403 854 179 (A/Prof Buttery)

Project Description: Direct clinical relevance: medium/high. Hands-on learning opportunities: general practice and public health datasets, real-time extraction and upload programming, signal detection methodologies.
In 2010, one of the seasonal influenza vaccines had an unacceptable rate of fever and febrile convulsions, resulting in at least one child with severe neurological sequelae. This project will test whether using pooled GP presentation data extracted from GP software can act as an 'early warning system', allowing potentially unsafe vaccines to be identified as soon as possible, minimising harm to the public.

Research Theme: Cell Therapy and Regenerative Medicine

159. Cell-based therapy for the ex vivo reconditioning of donor lungs prior to lung transplantation

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Prof Graham Jenkin, Dr Rebecca Lim (Monash University); Prof Andrew Fisher, Dr Lee Borthwick (Newcastle University, UK)

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Phone: 03 8572 2801 (Prof Jenkin)

Project Description: An opportunity exists to undertake a collaborative program of research, jointly at Monash University and Newcastle University, UK, under the auspices of the Monash-Newcastle Partnership Alliance. The project would be suitable for BMedSc Hons and/or PhD students. The research program brings together the therapeutic potential of placental derived stem cells and their conditioned media, developed at Monash, with the platform offered by ex vivo lung perfusion (EVLP) to ameliorate lung injury and inflammation in donor lungs before transplantation, developed at Newcastle. The research will involve in vitro cell and tissue culture and perfusion experiments to ascertain the timing, dose and nature (cells or conditioned media) of this novel biological therapy during EVLP to reduce inflammation, endothelial injury and immunogenicity of donor lungs immediately before organ transplantation. This approach could revolutionise ex vivo organ perfusion procedures and significantly increase the conversion rate of unusable to suitable donor lungs for increased lung transplant activity, protect against primary graft dysfunction and improve outcomes of this life-saving intervention.

160. Do cord blood stem cells reduce cerebrovascular brain injury?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Suzie Miller, Dr Margie Castillo-Melendez, Prof Graham Jenkin, Dr Courtney McDonald

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Phone: 03 8572 2796 (A/Prof Miller), 03 8572 2803 (Dr Castillo-Melendez)

Project Description: Babies that are born preterm are at the greatest risk of developing cerebral palsy. Indeed, up to 50% of children with cerebral palsy were born preterm. It is now appreciated that the parents of many Australian children with cerebral palsy are taking their children overseas to undertake cord blood stem cell therapy, despite a lack of published data that such therapy will be beneficial. We have identified that a principal component of brain injury in the preterm brain is instability of the blood vessels, which allows inflammatory and other blood products to enter the brain and damage cells. This project will examine whether cord blood stem cells can protect blood vessels within the brain, and in turn prevent brain injury. This project utilises brain tissue that has already been collected and does not require the student to undertake animal work.

161. The effects of cord blood stem cells on the lungs following fetal inflammation

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr Beth Allison, A/Prof Suzie Miller, Prof Graham Jenkin, Ms Madison Paton

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Phone: 03 8572 2488 (Dr Allison), 03 9902 2796 (A/Prof Miller)

Project Description: Intrauterine inflammation is recognised as a major cause of preterm birth and pulmonary complications in the developing lung. This study aims to examine whether human amnion epithelial cells (hAECs) can be used as a potential therapeutic agent to reduce lung injury induced by inflammation (lipopolysaccharide) in preterm fetal sheep. This project will utilise techniques to investigate lung injury, such as lung histology, inflammatory assays, RT-PCR, western blotting and stem cell tracking.

162. Isolation and banking of cord blood stem cells and placental tissues for future clinical therapies

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Prof Graham Jenkin, A/Prof Suzie Miller, Prof Mark Kirkland, Dr Courtney McDonald, Dr Margie Castillo-Melendez

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Phone: 03 8572 2801 (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), haematopoietic 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.

163. Isolation and expansion of umbilical cord blood stem cells for regenerative medicine

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr Abhilasha Tiwari, Prof Graham Jenkin, Dr Courtney McDonald, A/Prof Mark Kirkland (Deakin University)

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Phone: 03 8572 2801 (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 contain 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 the lives of people suffering from blood disorders, cancers and autoimmune diseases. The experiments will include cell culture and molecular biology techniques, and transplantation of UCB stem cells to mice to determine their efficacy.

164. Human amnion epithelial cells to prevent adverse outcomes of perinatal inflammation

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: A/Prof Tim Moss, Prof Jane Pillow (University of Western Australia)

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Phone: 03 8572 2821 (A/Prof Moss)

Project Description: Many preterm babies are exposed to inflammation before birth. This inflammation affects development and can cause life-threatening illness in newborns. The anti-inflammatory properties of epithelial cells from the amniotic membrane may be able to reduce the inflammation, normalise development and prevent illness in these babies. The aim of this project is to determine the effects of human amnion epithelial cells on inflammation, injury and development, using tissues from preterm lambs. Individual projects may focus on particular aspects of development, inflammation or injury, using tissues including the brain and respiratory, immune and gastrointestinal systems.

165. How do umbilical cord blood stem cells reduce neuroinflammation and perinatal brain injury?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Courtney McDonald, A/Prof Suzie Miller, Prof Graham Jenkin

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Project description: Cerebral palsy (CP) is the most common cause of physical disability in children and there is no cure. Inflammation is known to play a key role in the development of brain injury; however the immune cells or mechanisms that are involved in perinatal brain injury (which leads to CP) are not well understood. This proposal will explore a new therapy that holds much promise for treating children with CP: stem cells isolated from umbilical cord blood. Using a rodent model of perinatal brain injury, in this project we will explore the mechanism of how specific cord blood stem cells can reduce brain inflammation and damage caused by hypoxia-ischemia, an event known to lead to cerebral palsy. This project will also use cutting-edge technology, including magnetic resonance imaging techniques, to track the fate of umbilical cord blood stem cells in the brain, and extensive multi-colour flow cytometry to examine the mechanisms by which stem cells reduce perinatal brain injury.

166. Do cord blood stem cells promote neurorestoration in preterm brain injury?

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Suzie Miller, Dr Margie Castillo-Melendez, Prof Graham Jenkin, Dr Courtney McDonald

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Phone: 03 8572 2796 (A/Prof Miller), 03 8572 2803 (Dr Castillo-Melendez)

Project Description: One of the most devastating pathologies that occurs in preterm births is brain haemorrhage, which increases an infant's probability of being diagnosed with cerebral palsy, emphasising the involvement of the cerebral vasculature in the aetiology of neonatal brain injury. It is now appreciated that the parents of many Australian children with cerebral palsy are taking their children overseas to undertake cord blood stem cell therapy, despite a lack of published data that such therapy will be beneficial. Umbilical cord blood (UCB) represents a useful source of blood stem cells. UCB is enriched with a number of different progenitor cells, thus it has the potential to generate a variety of cell types and produce restoration of the brain via the formation of new blood vessels (angiogenesis) and the generation of new neurons (neurogenesis) and synapses (synaptogenesis). In adult brain injury, the generation of new blood vessels is known to facilitates neuro-restorative processes, including neurogenesis and synaptogenesis, which in turn lead to improved functional recovery. This project will determine if UCB cell transplantation prevents injury in the preterm brain by stimulating the brain restorative capacity – by promoting angiogenesis, neurogenesis and synaptogenesis. This project utilises brain tissue that has already been collected and does not require the student to undertake animal work.

167. Stem cells and tissue scaffolds

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Tony Goldschlager, Prof Graham Jenkin

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Project Description: In these studies, we are investigating the suitability of novel biomimetic matrices to form tissue structures to produce biomimetic spinal discs for repair of discs damaged by trauma or degenerative processes. We will study the characteristics of biomatrices both in vitro and in vivo, in collaboration with the commercial company, Mesoblast. We will determine the appropriateness of our cellular scaffolds for the production of engineered tissues. We will determine the most appropriate polymer compositions and stem cell combinations that can be developed into the most viable scaffold for therapeutic use in clinical trials.

168. Stem cells and pregnancy: what women want

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Prof Euan Wallace, Prof Graham Jenkin

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Phone: 03 8572 2801 (Prof Jenkin)

Project Description: As a component of a program of stem cell and cell therapy research, the student will explore women's views about stem cell therapies and their application to their baby's health, using validated surveys. The project will be based at Monash Medical Centre, where the student will interview new mothers who have just had a baby at either Monash or Jessie McPherson Private Hospital, exploring their attitudes to the collection of cord blood stem cells and placental stem cells. Skills in questionnaire development, data analyses and bioethics will be gained in this project, as well as participation in stem cell research.

169. Activating the stem cell niche

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Rebecca Lim, Prof Euan Wallace

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Phone: 03 8572 2794 (Dr Lim)

Project Description: Amnion stem cells have reparative potential in the lung. It is yet unknown how they trigger the regenerative process to improve lung function. We will use an animal model to mimic chronic lung disease and determine how amnion stem cell treatment can awaken the stem cell niche in the lung. Various techniques will be employed, such as small animal surgery, stem cell culture, immunohistochemistry, ELISA, FACS, real-time PCR and western blotting. This project will provide valuable data on the mechanism of stem cell action as this work progresses to clinical trials.

170. Stem cell based nanomedicine

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Rebecca Lim, Dr Jean Tan

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Phone: 03 8572 2794 (Dr Lim)

Project Description: This project looks to characterise the exosomes released by different stem cell types and assess their potential for regenerative medicine, and thus possibly pave the way for cell-free therapies. This area of research is newly emerging and highly novel in the stem cell field. Techniques employed include stem cell isolation, mass spectrometry, bioinformatics, tissue culture, electron microscopy, molecular biology, real-time PCR and western blotting.

171. Treatment of critical limb ischaemia with stem cell based nanomedicine

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Jean Tan, Dr Rebecca Lim

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Project Description: Critical limb ischaemia (CLI) affects 15% of the population of every socioeconomic scale. Arteriosclerotic plaque build-up causes occlusion of oxygen and nutrient supply to the limb leading to tissue death, leaving amputation as the only option. Amnion stem cell derived nanoparticles have shown significant vasculogenesis potential, making them a viable source for therapy. We will use an animal model to mimic CLI and determine how naturally occurring nanoparticles released by stem cells can help revascularise necrotic limbs and prevent amputation.
Techniques involved include small animal surgeries, cell culture, MRI and SPECT imaging, immunohistochemistry, ELISA, FACS, real-time PCR and western blotting.

172. Therapeutic application of human amnion epithelial cells in allergic asthma

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Rob Bischof, A/Prof Tim Moss, Prof Euan Wallace

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Phone: 03 8572 2820

Project Description: Allergic asthma is a chronic inflammatory disease of the airways that has a significant impact on affected people of all ages. Human amnion-derived epithelial cells (hAECs) have stem cell-like properties, as well as possible anti-inflammatory or immunomodulatory characteristics that make them attractive as a potential cell therapy. The aim of this project is to investigate the therapeutic efficacy of airway hAEC administration, in blocking or reducing the asthmatic airway responses in a sheep model of asthma. These experiments will include whole-animal physiology, immunology, cell biology, microscopy and molecular biology techniques.
Keywords: asthma, inflammation, stem cell therapy

173. Amnion cells for the treatment of cerebral palsy

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: Dr Bryan Leaw, Dr Rebecca Lim, Prof Euan Wallace

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Project Description: Cerebral palsy affects 1 in 500 babies, and every 15 hours a baby is diagnosed with cerebral palsy. Cerebral palsy is a group of motor and cognitive impairments, where patients may never develop the ability to walk and experience delayed learning. Unfortunately, these symptoms are lifelong and there is no cure. Amnion cells are an exciting part of the emerging cell therapy field, and we have previously shown in other models that amnion cell administration results in reduced inflammation and cell death after brain injury. Using a new rat model of cerebral palsy, we will assess whether amnion cells have long-lasting protective effects, and for the first time assess whether they improve long-term motor and learning outcomes. This project involves small animal surgery and molecular techniques.

174. Tracking stem cells in vivo in regenerative medicine

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours

Project Leaders: Dr Courtney McDonald, Prof Graham Jenkin, A/Prof Tony Goldschlager, Dr Rebecca Lim, Prof Euan Wallace

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Phone: 03 8572 2801 (Prof Jenkin)

Project Description: We are exploring the use of human amnion epithelial cells, mesenchymal stromal cells and mesenchymal progenitor cells as cellular regenerative therapy for a variety of diseases, including bronchopulmonary dysplasia, chronic lung disease of the preterm infant, multiple sclerosis and spinal disc repair. This project will utilise novel labelling techniques, including MRI, that will allow us to track the migration profile of stem cells in real time.

175. Cord blood derived stem cells as therapy for brain and lung inflammation in preterm newborns

Theme: Women's, Children's and Reproductive Medicine

Suitability: Honours, PhD

Project Leaders: A/Prof Suzie Miller, Prof Graham Jenkin, Dr Margie Castillo-Melendez, Dr Courtney McDonald

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Phone: 03 8572 2801 (Prof Jenkin)

Project Description: Premature birth leads to lifelong complications of both brain and lung development. Cells isolated from umbilical cord blood have stem cell-like properties and other characteristics that make them attractive as a potential cell therapy. The aim of this project is to identify the effect of human umbilical cord blood cells on inflammatory responses of newborn preterm lambs. The experiments include whole-animal physiology, immunology, microscopy and molecular biology techniques.

RESEARCH THEME INDEX

This list of research themes can be used to locate projects associated with your area(s) of interest. (Note that, within this Student Project Book, the research projects have been listed within the Hudson Institute research centre they each belong to).

Another handy way of searching for projects is by conducting a 'Word Find' (CTRL + F) for any specific key words you are interested in, such as 'stem cells', 'oestrogen', 'synchrotron' or 'sequencing' within the digital version of this book.

You can find this digital version on our website at **http://hudson.org.au/students/student-projects/**

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