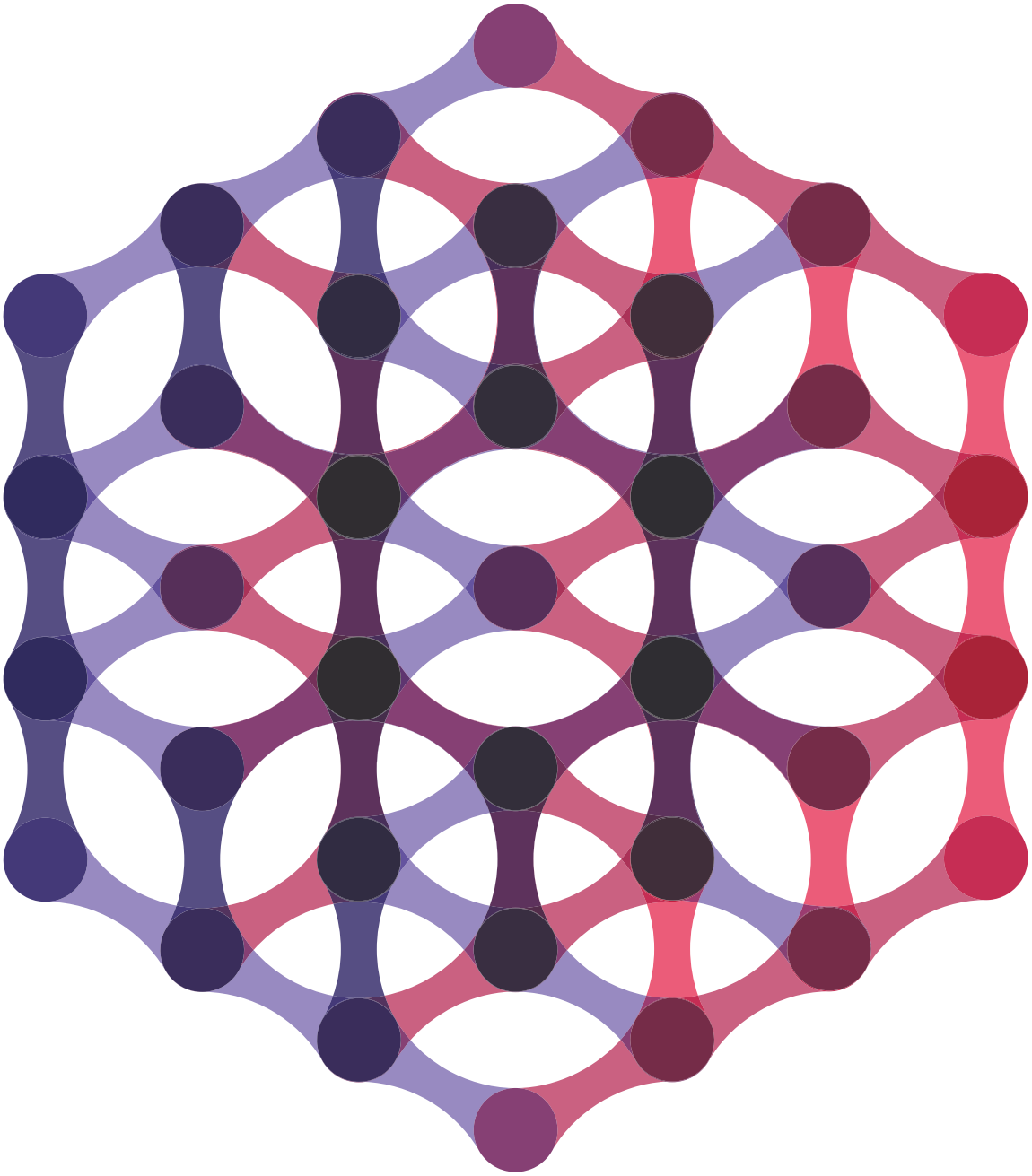
HUDSON
INSTITUTE OF MEDICAL RESEARCH



Student Research Projects

www.hudson.org.au

2016

CONTENTS

WELCOME FROM THE DIRECTOR

Professor Bryan Williams
Director, Hudson Institute of Medical Research

If you're passionate about medical research, the Hudson Institute is the place for you. Students play a critical role in Hudson research, making significant contributions to the Institute's research success and international reputation. We offer a diverse range of opportunities for ambitious and enthusiastic young scientists who are keen to start their careers at the forefront of biomedical science.

The Hudson Institute of Medical Research was officially launched in January 2014 with the joining of two of the most trusted names in medical research, Prince Henry's Institute (PHI) and the Monash Institute of Medical Research (MIMR). Now, with more than 450 leading research experts and postgraduate students, and access to state-of-the-art research platforms and facilities, the opportunities that this combined Institute represent are truly exceptional as we take our place as one of Melbourne's top medical research Institutes.

Hudson Institute's world-class scientists and clinicians are at the forefront of discovery and translational research, striving to improve health and quality of life across the entire lifespan, by advancing healthcare through an increased understanding of disease and its diagnosis, treatment and prevention.

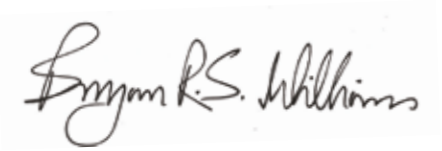
The Institute's excellence in biology, medicine and biotechnology is strengthened by our diverse, multidisciplinary research environment, which fosters collaboration and creates opportunities for unique insights and innovation.

It is a very exciting time for the Institute. In October 2015, the Hudson Institute will open its new, $84 million, state-of-the-art Translational Research Facility with partners Monash Health and Monash University. The facility will co-locate research, clinical and technological platforms to allow the Institute's researchers to leverage the practical knowledge of our clinical colleagues to ensure the most pressing diseases are being investigated and to effectively translate ground-breaking discoveries into patient treatments. This vision for an end-to-end story of health innovation will transform the Institute's research capability and enable researchers to make a far greater impact on health.

The Institute drives innovative, cutting-edge research programs through six specialised research-themed centres, which strive to respond to Australia's key health priorities:

- Cancer
- Genetic Diseases
- Immunity, Inflammation and Infectious Diseases
- Reproductive Health
- Fetal, Neonatal, Children's and Women's Health
- Endocrinology and Metabolism

We look forward to welcoming new students and fostering the talents of the next generation of researchers and clinicians in 2016. The following pages explain the application process to study at Hudson Institute and the wide range of research projects available in 2016.



Professor Bryan Williams, PhD, (Hon) FRSNZ, FAA

Why Study at the Hudson Institute?

The Hudson Institute prides itself on offering a stimulating, nurturing environment for its students. Currently there are over 150 students enrolled in Honours, Masters and PhD courses.

The Hudson Institute provides unique opportunities for students, such as:

- Research training in an outstanding dedicated research institution
- One-on-one student-to-supervisor contact in a nurturing, stimulating environment
- Mentoring by internationally recognised scientists
- Supervisors in perinatal physiology, sleep physiology, molecular and cellular biology, endocrinology, reproductive health, immunology, biochemistry, genomics, stem cells and clinical research
- Direct access to patients and clinicians through close collaborations with partnering organisations, including Monash Health
- Opportunities to present your research nationally and internationally
- Students have access to state-of-the-art facilities accommodating sophisticated approaches to gene targeting, genomic, proteomic and high-content analysis of cell and animal biology
- The most advanced stem cell technologies, embryo microinjection gene arrays, laser capture micro-dissection, confocal microscopy and cell imaging ensure research is carried out using the latest cutting-edge equipment
- Clinical facilities include access to the largest Obstetric and Neonatal Intensive Care Units in Victoria and the only dedicated Paediatric Sleep Clinic in the state
- Location at Monash Medical Centre offering unique opportunities for combining clinical and basic science research
- Well-established and supportive Student Honours and Postgraduate committees and student social clubs

Courses Available

The Hudson Institute has an excellent reputation for its student programs. Firstly and most importantly, carefully choose the area(s) of research that interest and excite you. Thoroughly read this handbook and visit the Hudson Institute website www.hudson.org.au to identify the Research Centre(s) that have the project(s) you are most interested in. Then call or email the relevant contact and arrange a time to discuss their research and meet their team. You can do this any time throughout the year. Don't forget to make the most of our Student Open Day, which is held in August each year. It's a great way to explore the wide range of potential projects available and view the facilities and technologies available at the Hudson Institute. Students are encouraged to further their qualifications and experience through the following degrees:

Honours programs:

- Bachelor of Science (Honours) – including Bachelor of Biotechnology (Honours)
- Bachelor of Biomedical Science (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**

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

External Applications (non-Monash University students)

Applications from external students (both international and Australian) are very welcome. 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 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.sci.monash.edu.au/undergrad/honours/apply.html**

The completed form is submitted to the Science Faculty Office, Building 19, Monash University, Clayton, for Monash students in early November (check the website for exact date).

Bachelor of Biomedical Science (Honours)

Monash applicants: Students must complete the Bachelor of Biomedical Science or one of the associate programs. An average of at least 70% across BMS3021, BMS3042 and the two highest level 3 electives (12 credit points) is required for consideration.

Non-Monash applicants: Students must complete a degree comparable to the Bachelor of Biomedical Science offered by Monash University. The entire academic record will be considered with an emphasis on the year 3 unit outcomes. As a guide, a comparable program in a group of 8 University would need an average of at least 70% in the year 3 subjects. Students will be required to provide certified documentation of their results and course completion. When submitting an application, please submit the academic results achieved to date.

The Biomedical Research Project component of your honours year (BMS4100) is run by 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 downloaded from: **http://www.med.monash.edu.au/biomed/honours**
You are required to upload your completed BMS (Hons) application form in portable document (pdf) into E-Admissions by mid-November. Please check the website above for the specific date.

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 2015. 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, allowing an accelerated degree. 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 from the Online Handbook:
http://www.monash.edu.au/pubs/handbooks/courses/0041.html

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 from the Online Handbook:
http://www.med.monash.edu.au/psych/course/4thyear/bbns-honours.html

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 PhD program includes a 3 month coursework 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 coursework 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, Progress Review, Final Review 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 Profiles

Current Students

Amy Winship
Centre for Reproductive Health

Amy has completed Honours and is currently undertaking the third year of her PhD

I began my PhD with Associate Professor Eva Dimitriadis in 2012 in the Embryo Implantation Research Group at the Hudson Institute. After completing a Bachelor of Science with Honours in Immunology at Monash University, the Hudson was an attractive independent medical research institute with world-leading reproductive scientists and facilities. Proximity to Monash Medical Centre means we have access to precious human samples that enhance the translational potential of our findings in the lab. I have attended local, national and international conferences to share my findings and won numerous presentation and travel awards. I have been the student representative member for the Society of Reproductive Biology (SRB) and in 2013 I won the national SRB David Healy New Investigator Award. The strong academic environment at the Hudson promotes students to excel for a future in a career in medical research. Hudson also has a wonderful social environment, particularly for students. I have been a member of the student society, which runs functions and educational events to ensure the students are always engaged and happy. The Institute conducts internal events dedicated to students such as the 3 Minute Thesis Competition and the Postgraduate Student Symposium (PSS) to provide vital presentation, abstract and poster skills required for a career in research. In 2014 I received first prize at the PSS event.

Melinda Dolan
The Ritchie Centre

Melinda has completed Honours and is currently undertaking the third year of her PhD

I joined The Ritchie Centre in 2010 as an Honours student after completing my undergraduate degree (BSc) at Monash University, majoring in both pharmacology and physiology. I had never considered research until I undertook a fetal physiology unit run by The Ritchie Centre (now known as

BME3082 – Developmental and Fetal Physiology), where I approached Associate Professor Tim Moss about an Honours research project. After completing my Honours degree, I began my PhD with Associate Professor Moss and Dr Megan Wallace in 2011. The Ritchie Centre was a highly desirable place to begin a career in research because it is one of the leading Australian centres in perinatal research and has a very strong understanding and culture of support for students. Since joining, I have also discovered the great collaborative nature of the Institute. Throughout my time at the Hudson I have had the opportunity to present my work at a number of national and international conferences. There are great opportunities for involvement in student societies and representation, as well as organising small early career researcher conferences within my Centre.

Justine Olcorn
Centre for Reproductive Health

Justine has completed Honours and is currently undertaking the third year of her PhD

My association with the Hudson Institute began in 2010. After completing a Bachelor degree in biomedical science, I knew I wanted to embark on a medical research career. I completed my Honours degree in the Male Fertility Research Group and went on to begin a PhD with Drs Peter Stanton and Craig Harrison. My research has greatly benefited from the Institute's variety of techniques and platforms. Over the course of my PhD I have been given the opportunity to present at various conferences including the international World Congress of Reproduction, the National Society of Reproduction, and the Australian Society of Medical Research. I have also received numerous awards, including the Society of Reproduction Conference Oozoa award for the Best Student Oral Presentation and received a scholarship to attend the prestigious Frontiers in Reproduction course in 2014 at the Marine Biology Laboratory in Woods Hole, MA, USA. The main reason I decided to undertake my research at the Hudson Institute was to learn from world-renowned experts in an environment focused on driving research towards achieving health outcomes. In addition to my postgraduate studies, I have been involved in teaching second year biochemistry at Monash University and am a dedicated member of the fantastic Hudson Institute Student Society.

William Lee
Centre for Genetic Diseases

William is currently undertaking the third year of his PhD

I began my PhD in 2012 with Professor Justin St. John in the Centre for Genetic Diseases, investigating the impact of mitochondrial genetics on cellular fate in cancer and stem cells. The Hudson Institute has provided me with a highly stimulating working environment with world-leading scientists and access to cutting-edge core facilities. I received administrative support and guidance from the Postgraduate Committee to achieve my milestone goals. I have also enjoyed the social aspects of student life, which involve social events organised by the Hudson Institute Student Society and Hudson Institute Social Club, providing the benefits of interacting with scientists in other fields. Throughout my time at the Institute I have been given the opportunity to present at numerous conferences. I have also received an award from the National Stem Cell Foundation of Australia.

Postdoctoral Students

Dr Sebastian Stifter
Postdoctoral Researcher

Sebastian completed his PhD in the Centre for Innate Immunity and Infectious Diseases in 2015

Honours didn't satiate my hunger for research so I continued with a PhD. I was very much interested in biochemistry and molecular biology when I first started my science career and my project was heavily reliant on the same techniques that were used to produce recombinant biologicals such as insulin and interferon, which in the current pharmaceuticals market are multi-billion dollar products. It wasn't the prospect of money that interested me, but rather knowing the whole process from start to finish. My PhD entailed the production of a new interferon (IFN) called Interferon epsilon and the characterisation of its activities. Interferons are very potent molecules produced in huge quantities following viral infections. Interestingly, they're used in clinical settings to treat a number of diseases and malignancies such as Hepatitis C, melanoma and other cancers, and I spent a considerable amount of time producing IFN-epsilon in a 'test-tube' and then treating cells

with it to see how the cells behaved. Significantly, I was the first person in the world to produce this new molecule and develop a procedure for doing so in a very reproducible manner. In addition to producing IFN-epsilon, I showed that IFN-epsilon protein, unlike other interferons that are produced after virus infection, is expressed in the female reproductive tract. Of course my research wasn't a one-man show and a combined effort of our Research Group and our collaborators' led to a publication in Science—with more publications on the way. IFN-epsilon is currently making international headlines and is attracting some very serious research interest. I'm extremely proud to say I've done my PhD at the Monash Health Translation Precinct (MHTP) in the Hudson Institute's Centre for Innate Immunity and Infectious Diseases.

Dr Karinna Fyfe
Postdoctoral Researcher

Karinna completed her PhD in The Ritchie Centre in 2014

I completed my Bachelor of Medical Science (Hons) after my 4th year of medical school. I enjoyed my BMedSci project so much that I felt compelled to see the research through to its completion and undertake a PhD. I developed a particular interest in preterm infants who are born incredibly vulnerable to a vast range of different conditions and therefore stand to significantly gain from research directed at improvements in their management. My research involved investigating the increased risk of Sudden Infant Death Syndrome (SIDS) in infants born preterm. I measured a range of physiological variables while conducting sleep studies in preterm infants, primarily focusing on cerebral oxygenation, which provides an indication of blood supply to the brain during sleep. We discovered that preterm infants have significantly lower cerebral oxygenation during sleep, compared with infants born at term. Of even more significance, we showed for the first time that placing a preterm infant in the prone position (on their stomach) to sleep, causes a further drop in their cerebral oxygenation, which suggests that this may contribute to the increased risk of SIDS in preterm infants compared to full-term infants. Prone sleeping remains a major risk factor for SIDS and this important research provides further evidence to support safe sleeping guidelines for infants. I feel very lucky to have had the opportunity to conduct my research in an environment that is both supportive but also promotes a culture of research excellence. I can't recall a single conference or symposium in which a student from The Ritchie Centre didn't win a prize; the quality of work is exemplary! The quality and diversity of research, access to excellent facilities and the close working relationship with Monash Health, where I am currently an intern, ensures Monash Health Translation Precinct (MHTP) is perfectly placed to conduct exceptional translational research. At MHTP, clinicians and researchers are actively encouraged and supported to collaborate to ensure that research efforts are directed towards areas most in need.

Student Support Programs

Hudson Student Vacation Placement Program 2015-2016

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 2015-2016 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.

For further information please visit our website at: **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: Harriet Fitzgerald
Vice President: Kimberley D'Costa
Treasurer: Dean Popovski
Secretary: Paulo Pinares-Garcia

Centre Representatives:

- Centre for Reproductive Health (CRH): Justine Olcorn, Hannah Loke
- Centre for Endocrinology and Metabolism (CEM): Katharine Johnson
- Centre for Cancer Research (CCR): Heba Zahid, Catherine Cochrane, Dean Popovski
- Centre for Genetic Diseases (CGD): Vijesh Vaghjiani
- Centre for Innate Immunity and Infectious Diseases (CiiiD): Gavin Brooks, Aleks Guanizo
- The Ritchie Centre (TRC): Madison Paton, Paris Papagianis
- School of Clinical Sciences (SCS): Lara Bush, Riana Samuel

Award winners, PSANZ Annual Meeting 2014, L - R: Annie McDougall, Melinda Dolan, James Aridas and Courtney McDonald

CENTRE FOR CANCER RESEARCH

Centre Head: **Professor Bryan Williams**

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.

Current key areas of interest include:

- Links between innate immunity, inflammatory processes and cancer
- Role of embryonic signalling pathways in cancer, and the targeting of these pathways with novel therapies
- Cell signalling pathways involved in tumour survival and growth, and the development of monoclonal antibodies to treat glioma and other cancers
- Role of integrin-linked kinase in cell migration and oncogenesis
- Molecular pathways involved in the metastasis of tumours, including colorectal, ovarian, prostate and bladder cancers
- Role of 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 PROJECTS

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

Suitability: Honours/Doctorate
Location: Level 1, Hudson Institute of Medical Research
Project Leader: **Dr Jason Cain**
Email: *jason.cain@hudson.org.au*

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.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Bryan Williams, Dr Afsar Ahmed**
Email: *bryan.williams@hudson.org.au*
afsar.ahmed@hudson.org.au

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-β. 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.

3. Modulating microRNA levels in inflammation and cancer

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Michael Gantier, Dr Jonathan Ferrand**
Email: *michael.gantier@hudson.org.au*
jonathan.ferrand@hudson.org.au

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.

4. Regulation of inflammation in cancer

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Dakang Xu, Prof Bryan Williams**
Email: *dakang.xu@hudson.org.au*
bryan.williams@hudson.org.au

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.

5. Epigenetic control of inflammatory disease

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Dakang Xu, Prof Bryan Williams**
Email: *dakang.xu@hudson.org.au*
bryan.williams@hudson.org.au

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.

6. Development of broad spectrum antivirals

Suitability: Honours/Master by Research
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Anthony Sadler, Prof Bryan Williams**
Email: *anthony.sadler@hudson.org.au*
bryan.williams@hudson.org.au

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 novel target identification and a development pipeline for broad-spectrum antivirals.

7. Kinase capture

Suitability: Honours/Master by Research
Location: Hudson Instituteof Medical Research
Project Leaders: **Dr Anthony Sadler, Prof Bryan Williams**
Email: *anthony.sadler@hudson.org.au*
bryan.williams@hudson.org.au

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 processes. The project will establish and validate an expression library of the human kinome, before endeavouring to identify kinases of orphan protein substrates.

8. Role of PKR in obesity

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Anthony Sadler, Dr Daniel Gough**
Email: *anthony.sadler@hudson.org.au*
daniel.gough@hudson.org.au

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.

9. Does Myc over-expression drive platinum resistance in small cell lung cancer?

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Daniel Gough, Dr Jason Cain, Dr Christine White**
Email: *daniel.gough@hudson.org.au*
jason.cain@hudson.org.au
christine.white@hudson.org.au

Project Description: Lung cancer is the most lethal form of cancer. 70% of small-cell lung cancer (SCLC) patients present with inoperable disease. Initially platinum based chemotherapy is very effective, but almost all patients rapidly relapse. After relapse SCLC is uniformly fatal. Nearly 30% of SCLC patients over-express the MYC oncogene, and MYC over-expression correlates with increased platinum resistance. In this project we will use our newly developed mouse model of MYC driven SCLC and primary patient tissue to define the role for MYC in SCLC and platinum resistance.

10. Is STAT3 a tumour suppressor in osteosarcoma?

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Mr Daniel Gough, Dr Jason Cain**
Email: *daniel.gough@hudson.org.au*
jason.cain@hudson.org.au

Project Description: Osteosarcoma is the most common form of bone cancer, and is typically associated with loss of p53, Rb and widespread genomic instability. STAT3 is a protein that when over-activated is typically associated with tumour progression and worse outcomes. However, we have found the removal of the STAT3 gene from osteosarcoma cell lines makes them form more aggressive tumours. This project will use molecular biology, biochemistry and mouse models of cancer to define the tumour suppressor role for STAT3 in osteosarcoma.

11. Regulation of STAT3 mitochondrial import and biogenesis

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Daniel Gough, Dr Daniel Garama**
Email: *daniel.gough@hudson.org.au*
daniel.garama@hudson.org.au

Project Description: Signal Transducer and Activator of Transcription (STAT3) is a key transcription factor required for cytokine signaling and growth and is crucial to life. Normal tissue homeostasis is maintained by the diverse role of STAT3 plays in the cell and any disruption to its function leads to constitutive over-expression, a trait found in most cancers. We recently found an additional role for STAT3 in mitochondria, where it is able to enter and regulate metabolism necessary for cancer. However, it is unclear how STAT3 controls mitochondrial activity. This project builds upon current research in the STAT Cancer Biology Laboratory, taking advantage of our suite of STAT3 mutants and cutting edge mass-spectrometry to define both the mechanism of STAT3 import and regulation of mitochondrial activity which are critical for the pathogenesis of up to 25% of human tumours.

12. STAT3 is a master regulator of β-cell function in type 2 diabetes

Suitability: Honours
Location: St. Vincent's Institute, Fitzroy, Melbourne
Project Leaders: **Dr Daniel Gough, Dr Esteban Gurzov**
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Project Description: The prevalence of obesity and type 2 Diabetes (T2D) has doubled in the past 30 years and now affects 360 million people worldwide. Autopsy studies have shown that β-cell mass is increased in non-diabetic obesity and is decreased in obese patients diagnosed with T2D. However, the molecular mechanisms leading to β-cell proliferation, dysfunction and death in these disease states are not well understood. Our studies suggest that the STAT family of transcription factors are activated in obese individuals and are required for β-cell function. This project will use human tissue, mouse models and cell culture systems to identify the role for STAT3 in β-cell function under diabetic conditions.

13. Inhibition of microRNA-155 in inflammation

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Claire McCoy, Prof Bryan Williams**
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Project Description: microRNAs (miRNA) are small RNA molecules that play essential roles in fine-tuning gene expression required for all functional responses in the cell. One particular miRNA, miR-155 is required for immune cell function, promoting an inflammatory response upon pathogen invasion. miR-155 is found overexpressed in many autoimmune pathologies such as multiple sclerosis, arthritis and inflammatory bowel disease. It is therefore essential that miR-155 expression is switched off appropriately to limit disease pathology. We have discovered that the anti-inflammatory cytokine IL-10 potently inhibits miR-155 expression in innate immune cells. This project aims to uncover novel downstream targets of the IL-10/miR-155 signalling axis and the role of these targets in autoimmune disease.

14. Investigating a Role for the Hedgehog Signalling Pathway in Bone Development and Disease

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Jason Cain, Prof Neil Watkins**
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Project Description: Hedgehog (Hh) signaling 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.

15. Interrogation of MYC Functions in Neural Development and Cancer

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Jason Cain, Dr Daniel Gough**
Email: *jason.cain@hudson.org.au*
daniel.gough@hudson.org.au

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. Utilizing 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.

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

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Maree Bilandzic, Dr Andrew Stephens, Dr Adam Rainczuk**
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Project Description: We have identified novel molecules expressed during the early events of ovarian cancer invasion to healthy tissue. We hypothesize that these molecules are key to the metastatic process, and by specifically disrupting their expression we will disrupt the invasion process. This work will seeks to develop new therapeutic strategies to block ovarian cancer metastasis and the formation of metastatic nodules.

17. Understanding chemoresistance in ovarian cancer cells

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Maree Bilandzic, Dr Andrew Stephens, Dr Adam Rainczuk**
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Project Description: Chemoresistant disease is the underlying cause of most deaths from ovarian cancer. This project uses primary ovarian cancer cells from patients at first presentation (no chemotherapy) and patients with recurrent disease (following chemotherapy) to determine which proteins control the acquisition of chemoresistance. The project aims to uncover novel ways of sensitizing chemoresistant ovarian cancer cells to chemotherapeutics.

18. Design and development of new diagnostic tests for the early detection of ovarian cancer

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Andrew Stephens, Dr Maree Bilandzic, Professor Magdalena Plebanski, Dr Adam Rainczuk**
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adam.rainczuk@hudson.org.au

Project Description: Ovarian cancer has the highest mortality rate of any gynaecological cancer, primarily due to the difficulty of detecting early stage, low volume disease. A diagnostic strategy to identify pre-metastatic ovarian lesions will significantly reduce mortality rates for this disease. We have identified a number of tumour-associated antigens, recognized by circulating auto-antibodies, in patients with early-stage ovarian tumours. The well-established ability of cancer patients to raise an anti-tumour immune response - often at a preclinical stage - makes these antigens excellent candidates for the design and development of new biomarker-based tests. This project will validate the expression and examine the biological roles of these antigens in ovarian cancer, and develop specific assay techniques for their measurement. The data obtained will drive the development of novel diagnostic and prognostic tools for improved cancer detection and management. Techniques will include molecular biology, cell culture, proteomics, immunoassay, immunohistochemistry and western blotting.

19. Regulation of anti-tumour immunity through the post-translational processing of chemokines

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute/Alfred Hospital
Project Leaders: **Dr Andrew Stephens, Professor Magdalena Plebanski**
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magdalena.plebanski@hudson.org.au

Project Description: Ovarian cancers typically exhibit an immunosupressed environment, where decreased T-cell infiltration into tumours is significantly correlated with worsened prognosis. We recently identified a new mechanism of immune suppression in ovarian cancers, whereby S9B/DPP4 serine proteases can modify chemokine signaling in tumours to influence the anti-tumour immune response.
This project will demonstrate proof-of-principal in vitro for this mechanism, and build on existing *in vivo* data testing the therapeutic use of targeted, small molecule inhibitors as a novel ovarian cancer therapy. Techniques: cell culture, *in vivo* imaging, flow cytometry, animal surgery, western blotting, immunohistochemistry and mass spectrometry imaging.

20. Identification of novel DPP9 inhibitors

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Andrew Stephens, Associate Professor Mark Gorrell (University of Sydney), Dr Adam Rainczuk**
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adam.rainczuk@hudson.org.au

Project Description: We have identified >100 new substrates of the enzyme DPP9, a protease involved in metabolism, immune function and possibly in the pathogenesis of several tumour types. Our data suggest the presence of an inhibitory factor present in the nucleus of cells. This project will identify and characterize this DPP9 inhibitor, with a view to the development of new DPP-targeted therapeutics. Techniques include HPLC, enzyme assay, mass spectrometry, cell culture and immunocytochemistry.

21. Nuclear Receptor Pharmacology

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **A/Prof Colin Clyne, Dr Chantal Magne Nde, Dr Kevin Knower**
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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.

22. Understanding resistance to breast cancer therapies

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **A/Prof Colin Clyne, Dr Chantal Magne Nde, Dr Kevin Knower**

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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.
We have identified a novel protein (of unknown function) that becomes activated in breast cancers that have developed resistance to tamoxifen. We have shown that this protein amplifies the effects of oestrogen - making breast cancer cells more responsive to the hormone, and increasing their ability to divide and spread. This effect may make cells less responsive to tamoxifen, thereby contributing to the development of resistance. This project aims to understand how this protein modulates oestrogen action at the molecular level and determine its potential as a marker to identify patients who may not respond well to tamoxifen.

23. Oestrogen Regulation in Breast Cancer

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Kevin Knower, Dr Colin Clyne**

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Project Description: Local oestrogen production within the breast is critically important for breast cancer progression. While the genetic factors that contribute to estrogen production are fairly well understood, epigenetic factors are much less well studied. Understanding these factors is critical to the development of tissue-specific strategies to inhibit this process. Development of breast cancer is characterised by a variety of genetic lesions including gene amplifications and deletions, point mutations, chromosomal rearrangements and overall aneuploidy. One of the most common molecular alterations in cancer is epigenetic change. Epigenetics describes a trait that is heritable, yet not based upon a change in primary DNA sequence. These epigenetic changes occur at a higher frequency than genetic changes, occur at defined regions in a gene, and most importantly are reversible upon treatment with pharmacological agents. DNA methylation is one well-known epigenetic mechanism that has a clear synergy with alterations in gene regulation that is associated with the onset of a developing cancer. We have shown that aromatase is under epigenetic regulation in breast cells and are currently expanding this theme to investigate the epigenetic regulation of key genes involved in estrogen synthesis. This project aims to identify changes in epigenetic status between normal and cancerous tissue to give a clearer understanding and development of future pharmacological agents.

24. Nuclear receptors and their functions in breast cancer stroma: Identification of novel therapeutic targets

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Kevin Knower, Dr Colin Clyne**

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Project Description: Breast cancer is a classical example of hormone-dependent malignancy. This is underlined in post-menopausal women where two-thirds of breast cancers are oestrogen receptor (ER) positive. Understanding the importance of the sex hormone oestrogen and the action of the ER in the genesis and progression of breast cancer has led to valuable endocrine therapies. Determining the levels of nuclear receptors (NRs) such as ER and the progesterone receptor (PR) has thus been central to breast cancer management for over 40 years. However, endocrine therapy resistance or the treatment of ER- and/or PR-negative tumours remains current day challenges. The necessity of identifying new therapeutic targets is paramount and while NRs such as ER and PR have proven beneficial, other NR super family members have been demonstrated to play key roles in breast cancer and offer alternative preventative targets. The stromal compartment of the breast is well established to play many roles in tumour progression. Furthermore, recent evidence has highlighted the potential of the tumour stroma as a target for cancer therapy. Despite this, the action of NRs in the tumour stroma is poorly understood. Through our current research, we have identified a distinct expression profile of all 48 members of the NR superfamily in ER-positive tumour stroma and found a number of these NRs as having altered expression compared to normal (Pubmed ID: 24122391). This project focuses on newly identified differentially expressed NRs as an entry point to retrieving their function in the ER-positive tumour stroma, their role in oestrogen biosynthesis, their influence on neighbouring epithelial cells and their viability as a therapeutic target.

25. Role of NF-κB in haematological malignancies

Suitability: Honours/Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Ashish Banerjee, Dr George Grigoriadis**

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george.grigoriadis@monash.edu

Project Description: Project description: The alternate NF-κB pathway is increasingly being recognised as an important player in chemo-resistance 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 that 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.

26. Role of bone marrow inflammation in the progression of myelodysplastic syndrome

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr George Grigoriadis, Dr Ashish Banerjee**

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Project Description: Myelodysplastic syndrome (MDS) is a group of diseases characterised by ineffective haematopoiesis, bone marrow dysplasia resulting in peripheral cytopenias in one or more myeloid lineages associated with transformation to AML. MDS patients have been purported to have a pro-inflammatory bone marrow environment that is believed to support the growth of the malignant clone and therefore plays a crucial enabling role in disease progression. We have found that inhibiting the NF-κB pathway dampens inflammation resulting in improved haematopoiesis in MDS patients. This project represents the interface of basic and translational research as findings from this study can be directly applied to clinical trials.

27. Iron chelation therapy to overcome chemo-resistance in haematological malignancies

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Ashish Banerjee, Dr. George Grigoriadis**

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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 chemo-resistance 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.

28. The cross talk between NF-κB and Stat3 in B cell homeostasis and function

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Ashish Banerjee, Dr Raffi Gugasyan, Dr Daniel Gough and Dr George Grigoriadis**

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Project Description: Gain of function mutations in Stat3 has 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-ÎºB 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.

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

Suitability: Honours/Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Professor Terrance Johns, Dr Sameer Greenall**

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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 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.

30. Evaluating new therapeutic targets for Diffuse Instrinic Pontine Glioma (DIPG)

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Jacqueline Donoghue, Professor Terrance Johns**

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Project Description: DIPG is one of the most aggressive and lethal paediatric brain cancers, and there are currently no suitable treatments or cure. Many children die within one year of diagnosis and some within weeks. We propose to develop several novel therapeutic strategies for DIPG using patient derived cell lines. We will be evaluating kinase inhibitors, HDAC inhibitors and transcription inhibitors to determine the best combinations for therapy. We will also evaluate the mechanisms of resistance in several *in vitro* and *in vivo* models of DIPG.

31. Investigating the genomic landscape of childhood cancer

Suitability: Honours/Master by Research Doctorate

Location: Genetics and Molecular Pathology laboratory at Monash Health and new laboratory space within the Monash Health Translation Precinct.

Project Leaders: **A/Professor 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.

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

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Kristy Brown, Jon Oakhill (SVI)**

Email: *kristy.brown@hudson.org.au*

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 3 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.

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

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Kristy Brown, Associate Professor Richard Ferrero**

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richard.ferrero@hudson.org.au

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 and 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.

CENTRE FOR ENDOCRINOLOGY AND METABOLISM

Centre Head: **Professor Peter Fuller**

The complex endocrine system impacts all aspects of health and disease. As a pre-eminent Centre for endocrinology research originating from Prince Henry's Institute, our laboratories undertake basic and clinical research. Our goal is to improve understanding of the role of hormones in human biology and disease to tackle key health challenges facing Australian and global communities, including reproductive health, bone health and cancer metastasis, cardiovascular disease, endocrine cancer and obesity. Clinical translation of these findings to improve diagnosis, therapeutic intervention, and prevention of disease remains a key focus for the group.

Key areas of interest:

- The identification of novel pathways to promote bone growth and limit bone destruction, to improve treatment and management of bone disease such as arthritis and osteoporosis and the spread of cancer to bone.
- The TGF-β family and the mechanisms that govern its regulation and impact on biological activity, including wound healing, immune function, fibrosis and tumour progression.
- 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.
- 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 hormone 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 and regulation of reproductive hormones in obesity and breast cancer, particularly the impacts of obesity (adiposity) and its links to an increased risk of breast cancer development in menopausal women.
- 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.

RESEARCH PROJECTS

34. Understanding the signaling mechanisms for MR regulation of cardiomyocyte function in heart disease

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Morag Young, Professor Peter Fuller**

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Project Description: Project Description: This 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. Earlier studies have identified a number of attractive candidate downstream signaling intermediates that we wish to assess *in vivo* and *in vitro* to determine their specific role in the development of heart failure. These studies hope to identify novel therapeutic targets for a broad range of cardiovascular diseases that are cardiac selective and thus have fewer side effects. In addition to *in vivo* monitoring of animal disease models, techniques will include immunohistochemistry, cell culture, western blotting and RT PCR techniques.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Morag Young, Professor Peter Fuller**
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Project Description: Project Description: Nuclear receptors associate with coregulatory proteins in order to modulate gene transcription: These coregulators 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 coregulators from the heart and kidney and this project will characterize 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 coregulators in macrophage, validation as true coregulators and characterization of their activity in immune cells and is more suited to a PhD applicant.

This project will include a suit of molecular biology techniques, cell culture, western blotting and RT PCR.

36. To define the role of macrophage MR signalling in adipose tissue inflammation and glucose tolerance

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Morag Young, Professor Peter Fuller**
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peter.fuller@hudson.org.au

Project Description: Mineralocorticoid receptors (MR) play a pivotal role in regulating the macrophage inflammatory phenotype. Targeting the MR in macrophages using gene targeting in mice prevents inflammation and fibrosis in a range of diseases.

We have preliminary data to show that mice lacking the MR in macrophages are protected from glucose intolerance due to obesity. This project aims to identify the mechanisms of the protective effect by studying metabolic changes in fat, muscle and liver. This project will involve immunohistochemistry, high throughput RT PCR platforms, data base analysis, western blotting and cell culture techniques.

37. Molecular pathogenesis of granulosa cell tumours of the ovary

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Simon Chu, Professor Peter Fuller**
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peter.fuller@hudson.org.au

Project Description: Granulosa cell tumours (GCT) of the ovary are endocrine tumours that both make hormones 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 the tumours. Areas of current focus include the role of nuclear receptors including estrogen receptor-β (ERbeta) and PPARgamma, regulation of apoptotic pathways, the significance of activation of the NF-kappaB pathway observed in two GCT derived cell lines, the exploration of novel therapeutic strategies, the use of microarray analysis to identify paths and profiles of gene expression, and the use of next-generation sequencing to identify novel mutations involved in GCT pathogenesis.

38. Role of XIAP in Endocrine Cancer (Ovarian and Thyroid)

Suitability: Honours/Master by Research
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Simon Chu, Dr Michael Mond, Professor Peter Fuller**
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Project Description: The X-linked inhibitor of apoptosis (XIAP) is a member of a family of endogenous caspase inhibitors that act as antiapoptotic factors. XIAP is the most potent caspase inhibitor, blocking both intrinsic and extrinsic apoptotic signals through direct caspase binding. Due to its prominent ability to control cell death and elevated expression in human cancers, XIAP has become an attractive therapeutic target for novel anti-cancer treatment. Small-molecule inhibitors are in various stages of development, from preclinical to phase II clinical trials. XIAP has an important role in both ovarian cancer as well as in 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, novel therapeutic compounds with the ultimate goal of providing an essential pre-clinical, proof of concept approach for translation to the clinic.

39. Role of XIAP in normal ovarian folliculogenesis

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Simon Chu, Dr Ann Drummond, Professor Peter Fuller**
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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.

40. Mineralcortiocoid receptor regulation of gene expression: novel tissues and novel targets

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Peter Fuller, Dr Ann Drummond**
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ann.drummond@hudson.org.au

Project Description: The mineralcortiocoid receptor (MR) is best known for its involvement in the regulation of salt and water balance. However, non-classical tissues such as breast and ovary 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 vitro* and *in vivo* in these tissues. The role of this receptor in breast, breast cancer, ovary and ovarian cancer is emerging as a potentially important story. We have created tissue-specific transgenic knockout mice: mammary tissue knockouts and granulosa cell (ovary) knockouts, to explore this question.

41. Hormonal regulation of folliculogenesis

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leader: **Dr Ann Drummond**
Email: *ann.drummond@hudson.org.au*

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 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.

42. Structure - function relationships of the mineralcorticoid receptor

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Professor Peter Fuller, Dr Morag Young**
Email: *peter.fuller@hudson.org.au*
morag.young@hudson.org.au

Project Description: The mineralcorticoid 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 involve the use of yeast-2-hybrid screens, transactivation assays, structural analysis, mutation detection, comparative biology and transgenic mouse models.

43. Osteoporosis and Metabolic Bone Disorders

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Frances Milat**
Email: *fran.milat@hudson.org.au*

Project Description: We are currently involved in a variety of projects aimed at improving health outcomes in patients with metabolic bone disorders and osteoporosis. These projects include the optimisation of bone health in adults with chronic neurological disability, understanding osteoporosis in haemoglobinopathies, assessing risk factors for atypical femoral fractures, the evaluation and management of chronic kidney disease, mineral and bone disorders and metabolic bone disorders in pregnancy. Research projects are available in many of these clinical areas.

CENTRE FOR GENETIC DISEASES

Centre Head: **Professor Justin St. John**

Research at the Centre for Genetic Diseases (CGD) focuses on understanding the genetic and epigenetic causes of disease. We undertake our research using a range of innovative reproductive, developmental biology and stem cell models, and utilise the most up-to-date analytical approaches. Many of the diseases that affect us today originate from changes present at fertilisation, and are therefore known as inherited diseases. Although these include diseases caused by mutations to the genes we inherit from our parents, it is becomingly increasingly evident that diseases also arise from changes to other (non-coding) regions of DNA and to epigenetic regulators, which are factors that determine if and when a gene is expressed. These areas of research are providing explanations for how diseases, for which the cause was previously unknown, are transmitted from one generation to the next.

In our Centre, we have a major interest in determining how changes in copy number of a gene lead to disease, and identifying how non-coding regions regulate gene expression. In related studies, we are investigating how very early epigenetic marks in sperm and eggs are modulated during development, how they regulate gene expression in our children and the impacts on disease in subsequent generations produced by individuals who lack these modifications. We are also investigating how mutations to the maternally inherited mitochondrial genome, which is separate to the chromosomal genome, are transmitted from the mother to her children. This involves developing specific, assisted reproductive technologies to prevent the transmission of mutant mitochondrial DNA from one generation to the next. Additionally, we are determining how the complexes of the mitochondrial electron transfer chain are assembled and how mutations to its nuclear and mitochondrial DNA genes affect this process. We are also determining how mutations to other mitochondrial energy-generating pathways affect cellular function.

By understanding the underlying genetic and epigenetic mechanisms of disease, our work will provide a platform for the development of tomorrow's therapies and influence clinical practice.

Research Disciplines:
- Mitochondrial Genetics
- Biomedical Genomics
- Germ Cell Development and Epigenetics
- Molecular Basis of Mitochondrial Disease

RESEARCH PROJECTS

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

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Matthew McKenzie, Professor Justin St John**

Email: *matthew.mckenzie@hudson.org.au*
justin.stjohn@hudson.org.au

Project Description: Mitochondria oxidize sugars and fats by oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to generate energy for the cell. Defects in either of these two 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 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 ES 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.

45. MicroRNA regulation of mitochondrial function

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Matthew McKenzie, Prof Justin St John**
Email: *matthew.mckenzie@hudson.org.au*
justin.stjohn@hudson.org.au

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.

46. Why are Boys More Susceptible to attention-deficit hyperactive disorder (ADHD) than Girls?

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Joohyung Lee, Prof. Vincent Harley**
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vincent.harley@hudson.org.au

Project Description: Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric disorder in children, consisting of age-inappropriate symptoms of inattention, hyperactivity, and impulsivity. Whilst the exact cause is unknown, it is clear that ADHD is much more common in boys than girls with a ratio of 4:1. We hypothesise that the male specific Y-chromosome gene SRY is a factor involved in the susceptibility of boys to attention deficit-hyperactivity disorder (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.

47. De-masculinising the Male Brain

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Joohyung Lee, Prof Vincent Harley**
Email: *joohyung.lee@hudson.org.au*
vincent.harley@hudson.org.au

Project Description: The Y-chromosome gene, SRY, is widely expressed in the male brain, such as the substantia nigra, ventral tegmental area (VTA), pre-frontal cortex (PFC), and hippocampus. These brain regions, which control important functions such as goal-directed actions, attention, and learning and memory, are also sexually dimorphic. This project seeks to determine the relative contribution of SRY in 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 i) behaviour (ie. attention, memory, and goal-directed behaviours), neurochemistry (i.e. measurement of catecholamine levels and cell numbers), and gene-expression (RNA seq, ChIPseq).

48. Using three-dimensional in vitro porcine and bovine ovarian culture models to create an artificial ovary

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Yogeshwar Makanji, Dr David Nisbet, Professor Justin St. John**
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david.nisbet@hudson.org.au
justin.stjohn@hudson.org.au

Project Description: Many young female cancer patients undergo chemo or radiation therapy, which introduces a risk of infertility. The in vitro growth and maturation of the ovarian follicle, which is the basic functional unit of the ovary, provides the potential to preserve fertility by growing follicles in vitro and transplanting them back into the patient. Growth and maturation of porcine and bovine primordial follicles into large pre-ovulatory follicles, is essential to gaining insights into human folliculogenesis. Thus, the three-dimensional alginate in vitro follicle culture system is an excellent model to study the role of TGF-beta growth factors, energy metabolites and the physical microenvironment of the ovary.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Professor Justin St. John, Dr Yogesh Makanji**
Email: *justin.stjohn@hudson.org.au*
yogesh.makanji@hudson.org.au

Project Description: Mitochondrial DNA 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 mitochondrial DNA 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.

50. Manipulation of germline epigenetics and germ cell development using pharmaceuticals

Suitability: Honours/Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Patrick Western, Dr Kirsten Hogg**

Email: *patrick.western@hudson.org.au*
kirsten.hogg@hudson.org.au

Project Description: 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 germ line epigenetics and potentially the inheritance of epigenetic information remains unknown. This project will examine how epigenetic modifying drugs impact male germ cell development and the patterning of epigenetic information in the germ line. 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 epiegenetics will be measured using immunofluoresence, qRTPCR and flow cytometry. This project will identify new epigenetic modifiers that act in the germ line and pattern epigenetic information that is transmitted to the offspring. Understanding these processes is essential to understand how epigenetic information is transmitted to, and affects development in the offspring.

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

51. Signalling in male germ cell development, stem cell pluripotency and germ cell tumour formation

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Patrick Western, Dr Kirsten Hogg**

Email: *patrick.western@hudson.org.au*
kirsten.hogg@hudson.org.au

Project Description: Germ cells are specialised cells found in the developing testes and ovaries that form sperm in males, or oocytes (eggs) in females. Germ cell development underpins reproductive health and fertility throughout an individuals life, while sperm and oocytes transmit the parent's genetic and epigenetic information to the offspring. Germ cells therefore play multiple central roles in biology of the individual and the species. This project aims to determine the role of signalling in male germ cell development, stem cell pluripotency and germ cell tumour formation (testis tumours). Inhibitors that block specific signalling pathways will be used in *in vivo* and in an *ex vivo* organ culture system to determine the role of specific signalling pathways in male germ cell differentiation, pluripotency and germ cell tumorigenesis. By exploring germ-line development and the establishment and function of epigenetic information in the germ line, our research will contribute to understanding human disease, including various cancers and the development of novel drugs targeting epigenetic processes.

Techniques: Organ culture, flow cytometry, qPCR, immunofluorescence, advanced micro-imaging (eg. confocal microscopy)

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. 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 – providing immediate protection and sculpting the ensuing adaptive (sustained) immune responses. It initiates the inflammatory response and can modulate the development of inflammatory and autoimmune diseases. 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 preventing, diagnosing and treating infections such as influenza, HIV, chlamydia, inflammatory diseases such as gastritis and chronic obstructive pulmonary disease, and cancers of the stomach, lung, breast and reproductive tract.

Staff and students working in CiiiD have collective multidisciplinary expertise in molecular biology, signal transduction, protein interactions, cell biology, immunology, 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 nearly $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, J. Clinical Investigation, Nature Medicine and Cancer Cell.

Research Disciplines:

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

RESEARCH PROJECTS

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Professor Brendan Jenkins**

Email: *brendan.jenkins@hudson.org.au*

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.

53. Role of Toll-like receptors in stomach cancer

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Professor Brendan Jenkins**

Email: *brendan.jenkins@hudson.org.au*

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.

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Professor Brendan Jenkins**

Email: *brendan.jenkins@hudson.org.au*

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.

55. The role of NOD1 sensing in cell survival responses favouring H. pylori survival

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leader: **Associate Professor Richard Ferrero**

Email: *richard.ferrero@hudson.org.au*

Project Description: During cell division, Gram-negative bacteria remodel their cell walls, resulting in the release of low molecular weight fragments of peptidoglycan, known as muropeptides. These muropeptides are recognised by host cells via the actions of the innate immune molecule, NOD1, resulting in the induction of a pro-inflammatory signaling cascade. We have preliminary data suggesting that host-adapted H. pylori strains exhibit different muropeptide forms, thereby rendering them better able 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, however, these responses 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.

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

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leader: **Associate Professor Richard Ferrero**

Email: *richard.ferrero@hudson.org.au*

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 IFN-α and that, moreover, it plays a role in MHC class I presentation. Our laboratory has the first evidence suggesting that NLRC5 may also play an important role in regulating inflammation in response to chronic H. pylori infection. The overall aim of the project is to

investigate how NLRC5 regulates inflammation 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 knockout mice. The project will involve various techniques e. g. primary cell culture, cell transfection, mouse infection, histology, cytokine ELISA and qPCR.

57. Helicobacter pylori activation of innate immune responses via the "inflammasome"

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leader: **Associate Professor Richard Ferrero**
Email: *richard.ferrero@hudson.org.au*

Project Description: The NLRs consist of a family of cytoplasmic signalling molecules of the innate immune system that share certain structural features, yet each has its own specificity and functions. A subfamily of NLRs is involved in the formation of various types of signalling platforms, "inflammasomes", whose principal function is pro-inflammatory cytokine processing and responses (principally IL-1β and IL-18). Although H. pylori is known to induce such responses in host cells, the mechanism involved has yet to be determined. The aim of the project is to investigate the role of inflammasome proteins in H. pylori-induced inflammation. The project will involve various techniques e.g. primary cell culture, mouse infection, histology, cytokine ELISA, qPCR and immunoblotting.

58. Transport and innate immune properties of DNA within bacterial membrane vesicles

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leader: **Associate Professor Richard Ferrero**
Email: *richard.ferrero@hudson.org.au*

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. In prokaryotes, the release of outer MVs was first described nearly 40 years ago, yet the biological significance of these structures is only beginning to be appreciated. Amongst the many cell wall-associated macromolecules and proteins present in bacterial MVs, it appears that DNA is also present. This DNA was suggested to be involved in genetic exchange amongst bacteria. Besides its key role in the transmission of genetic information, it is now clear that DNA has potent effects on the innate immune system which has evolved multiple proteins to "sense" this macromolecule.

The aims of the project are to characterise the DNA present in bacterial MVs and to elucidate how this cargo is presented to intracellular DNA "sensors" of the host immune system. This project will involve various techniques, including cell culture, confocal imaging, transfection, cytokine ELISA and immunoblotting.

59. The role of the H. pylori virulence factor, CagM, in infection and inflammation

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leader: **Associate Professor Richard Ferrero**
Email: *richard.ferrero@hudson.org.au*

Project Description: A major virulence factor of the gastric pathogen, H. pylori, is a genetic locus known as the cag pathogenicity island (cagPAI). This locus codes for a secretion apparatus facilitating the delivery of bacterial effector molecules to, as well as responses in, host cells. It is generally thought that H. pylori strains carrying the cagPAI locus are more virulent. Our laboratory, however, has shown that H. pylori bacteria deficient in one of the cagPAI genes, cagM, colonise mice to higher levels than either wild type or cagPAI mutant bacteria. Microarray studies have identified genes whose expression is specifically regulated by H. pylori CagM. The aim of this study is to understand how this protein regulates host immune responses to facilitate bacterial colonisation. This project will involve a variety of techniques, including cell culture, mouse infection, cytokine ELISA and qPCR.

60. The inflammasome and hyperinflammation in emerging infectious diseases

Suitability: Honours, PhD
Location: Hudson Institute of Medical Research
Project Leader: **Dr Ashley Mansell**
Email: *ashley.mansell@hudson.org.au*

Project Description: We recently identified and characterized 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 characterized by excessive inflammation such as Ebola virus, SARS-Coronavirus, Dengue virus and Picornoviruses. 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.

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Dr Ashley Mansell**

Email: *ashley.mansell@hudson.org.au*

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 anti-viral 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).

62. Systems biology of innate immune signalling

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Professor Paul Hertzog**

Email: *paul.hertzog@hudson.org.au*

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

63. Innate immune responses regulating breast cancer metastases

Suitability: Honours, PhD

Project Leaders: **Prof Paul Hertzog, Dr Helen Cumming**

Email: *paul.hertzog@hudson.org.au*

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 this 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.

64. Investigation of a novel cytokine in the barrier function of the reproductive tract to protection against infections

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Dr Niamh Mangan**

Email: *niamh.mangan@hudson.org.au*

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

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Niamh Mangan, Dr Nollaig Bourke, Professor Paul Hertzog**

Email: *paul.hertzog@hudson.org.au*

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 and Chlamydia and possibly HIV. It is unique for several reasons: unlike conventional cytokines, IFN 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 FRT mucosa 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 IFNe in the development and progression of uterine and ovarian cancer.

66. Uncovering novel immune responses in the reproductive tract

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leader: **Dr Niamh Mangan**

Email: *niamh.mangan@hudson.org.au*

Project Description: Our lab has discovered a novel cytokine, interferon epsilon (IFNε), with potent protective properties against infections in the reproductive tract. The immune response in many mucosal organs has evolved specific features to deal with their novel characteristics, such as in the female reproductive tract, which has to be protected from infections and other diseases, yet remain tolerant for implantation and development of a foetus. Since the WHO estimates 1 billion Sexually Transmitted Infections (STIs) annually, it clearly remains a challenge to understand mucosal immunity in the reproductive tract and manipulate it to generate effective therapies and vaccines. The aim of this project is to characterise the expression profile of this IFNε, not just in the reproductive tract, but throughout the mucosal immune system and other tissues in the body. We will then determine how this new protein interacts with the mucosal innate and adaptive immune system in physiological and pathological conditions.
Techniques: immunohistochemistry, cell culture, analysis of immune cells by flow cytometry, functional assays of innate and adaptive cells including macrophages, DC, NK, T and B cells, and cytokine assays. This exciting research will result in increased knowledge of mucosal immunology and implications for new STI therapies, vaccines and diagnostics.

67. Structural – functional characterisation of type I interferon receptors and signalling pathways

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Nicky de Weerd, Prof Paul Hertzog**

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nicole.deweerd@hudson.org.au

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.

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Michelle Tate, Prof Paul Hertzog**

Email: *paul.hertzog@hudson.org.au*
michelle.tate@hudson.org.au

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.

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Nollaig Bourke, Prof Paul Hertzog**

Email: *paul.hertzog@hudson.org.au*
nollaig.bourke@hudson.org.au

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 which 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 utilize 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.

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

Suitability: Honours, PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Prof Phil Bardin, Dr Belinda Thomas**

Email: *belinda.thomas@monash.edu*

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.

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.

- **Endometrial Remodelling** – The intrauterine microenvironment of implantation; endometrial repair; embryo-maternal interactions via exosomes; tests for endometrial receptivity.
- **Embryo Implantation** – Embryo-maternal interactions; miRNA 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).
- **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 TGFβ superfamily of ligands and recently, Hedgehog signalling. Another focus on nuclear transport has identified a new mechanism by which spermatogenesis is regulated.

RESEARCH PROJECTS

71. SRY: A Risk Factor for Parkinson's disease in Males?

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Vincent Harley, Dr Joohyung Lee**
Email: *vincent.harley@hudson.org.au*
joohyung.lee@hudson.org.au

Project Description: Parkinson's disease (PD) is a debilitating neurodegenerative disorder, triggered by the death of dopamine neurons in the brain region known as the substantia nigra. Whilst the mechanisms underlying dopamine cell loss in PD, 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 the PD and to identify SRY as a novel target for neuroprotective therapy in male PD patients.

72. Y-chromosome; Neurodegenerative disorders; Dopamine - The biological basis of gender identity

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Vincent Harley, Dr Fintan Harte** (Monash Gender Clinic)
Email: *vincent.harley@hudson.org.au*

Project Description: Gender identity is the gender with which a person identifies. Studies suggest that gender identity is affected by genetic, prenatal hormonal or postnatal social determinants. We are investigating the role of genes in patients with gender identity disorders. This project involves undertaking genetic association studies in the world's largest cohort of male-to-female transsexuals. It focuses upon genes involved in sex hormone synthesis and signalling.

73. How are male and female brains different?

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Vincent Harley, Dr Joohyung Lee**
Email: *vincent.harley@hudson.org.au*
joohyung.lee@hudson.org.au

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.

74. Identifying the genes responsible for Disorders of Sex Development (DSD)

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Professor Vincent Harley**
Email: *vincent.harley@hudson.org.au*

Project Description: Disorders of sex development (DSDs), formerly intersex are congenital conditions where gonadal or anatomical sex is atypical. DSDs encompass a wide range of abnormalities, including hypospadias (abnormal urinary opening in males), gonadal dysgenesis (underdeveloped or imperfectly formed gonads), and ambiguous genitalia and sex reversal (ie 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/

75. FGF signalling and sex reversal

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Vincent Harley, Dr Stefan Bagheri-Fam**
Email: *vincent.harley@hudson.org.au*
stefan.bagheri-fam@hudson.org.au

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 which might be defective in DSD patients. Analyses of male and female markers will be carried out, as well as markers of FGF signalling. Training includes basic cell and molecular biology as well as: embryonic microdissection, whole mount/section *in situ* hybridisation and immunofluorescence.

76. Characterisation of novel gonadal targets of Sox9

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leader: **Professor Vincent Harley**
Email: *vincent.harley@hudson.org.au*

Project Description: For the majority of DSD cases the underlying genetic aetiology is unknown. In males Sox9 is a critica 'hub' gene involved in sexual development. We hypothesise that Sox9's downstream targets are also essential for gonadal development and mutated in DSD patients. By extensive data mining of gonadal microarrays, RNAseq, and SOX9 ChIPseq we have identified genes directly regulated by SOX9. These candidate genes are up regulated in XY mouse testis compared to XX ovaries during development and down regulated in sex reversed XY ovaries ablated for Sox9. We will perform detailed expression profiling in XX and XY embryonic 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.

77. ATR-X syndrome & gonadal development

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Vincent Harley, Dr Stefan Bagheri-Fam**
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stefan.bagheri-fam@hudson.org.au

Project Description: The ATR-X syndrome, an X-linked recessive developmental disorder affecting males, belongs to a growing list of disorders of sex development (DSD) which affect 1% of all newborns. Clinical features include mental retardation, alpha-thalassemia and skeletal and genital abnormalities. The focus of our work is to investigate the role of ATRX in gonadal development.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Associate Professor Mark Hedger, Professor David de Kretser**
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david.de.kretser@monash.edu

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.

79. Investigation of the novel phenotype of testicular macrophages

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **A/Professor Mark Hedger, Julie Muir**
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julie.muir@hudson.org.au

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.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Associate Professor Mark Hedger, Professor David de Kretser**
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david.de.kretser@monash.edu

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.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Associate Professor Mark Hedger, Professor David de Kretser**
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david.de.kretser@monash.edu

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 proinflammatory and immunoregulatory functions, but until now, the role of activin in testicular and epididymal inflammation has been very poorly investigated. This project examines activin and its binding protein, follistatin in regulating inflammation and fibrosis caused by infection and autoimmunity in the male tract. These studies will also assess the potential for exogenous follistatin to serve as a therapeutic intervention for these conditions. 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.

82. Uterine surface transformation for embryo implantation and IVF success

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute, Centre for Reproductive Health
Project Leaders: **Associate Professor Guiying Nie, Dr Sarah Paule**
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sarah.paule@hudson.org.au

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 localization 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.

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

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **A/Professor Guiying Nie, Dr Sarah Paule**
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Project Description: The uterus requires substantial remodeling 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 characterized 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.

84. Stress-related genes in pregnancy disease preeclampsia

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **A/Professor Guiying Nie, Dr Sonia Teoh**
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sonia.teoh@hudson.org.au

Project Description: Preeclampsia is a life-threatening disorder of pregnancy, characterized by a sudden increase in blood pressure and urine protein after 20 weeks of gestation in previously normotensive women. Preeclmapsia 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 preeclampsia is to terminate the pregnancy and deliver the baby often prematurely.

Although causes of preeclampsia are multi-factorial, it is well established that the placenta is sufficient and necessary to cause preeclampsia. It is also emerging that placental stress contributes to preeclampsia development. This project will investigate a number of stress-related factors in preeclampsia, with a long-term goal of developing early diagnosis and potential treatment for preeclampsia.

85. CSF3 actions on the endometrium: critical for embryo implantation into the womb

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Professor Lois Salamonsen, Dr Tracey Edgell, Dr Jemma Evans**

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jemma.evans@hudson.org.au

Project Description: We have identified that concentrations of CSF3 within the uterine cavity during the window of implantation has a negative impact on embryo attachment, and thus prevents a successful pregnancy. How CSF3 exerts these effects is unclear. This study will examine potential impact of prolonged CSF3 exposure on endometrial cells. Media and cell lysates will be collected from epithelial cell cultures post-chronic exposure to CSF3. Cell lysates will be examined by western blot to quantify the CSF3 receptor. The media will be examined for the presence/concentration of matrixmetalloproteinases (MMPS) and their inhibitors (TIMPS) using zymography and Luminex (multiplex ELISA) methodologies. Tight junction integrity will be assessed by transepithelial resistance.

86. Scratching the surface

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Jemma Evans, Professor Lois Salamonsen**

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lois.salamonsen@hudson.org.au

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 this 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.

87. CSF3 glycoforms and CSF3 receptor expression

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Professor Lois Salamonsen, Dr Tracey Edgell**

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tracey.edgell@hudson.org.au

Project Description: We have identified that concentrations of CSF3 within the uterine cavity during the window of implantation has a negative impact on embryo attachment, and thus prevents a successful pregnancy. We have identified that the endometrium of non-receptive women in either natural or ART cycles displays diminished CSF3 receptor. We hypothesise that the absence of this receptor and consequent failure of CSF3 signalling is a cause of endometrial based infertility. Manipulation of the receptor-ligand interaction may restore endometrial receptivity.
In this study multiple forms of CSF3 (non-glycosylated, glycosylated from CHO, and glycosylated from NEK cells) will be compared. Following incubation of endometrial epithelial cells with CSF3 the receptor expression/location will be compared by immunocytochemistry, and western blot densitometry of the receptor concentration made. Cell signalling pathway activation will be compared using western blot/luminex technology. The effect of each CSF3 type on attachment of trophectoderm spheroids (representative of human blastocyst) to the endometrial cells will be examined.

88. The obesity epidemic and its impact on fertility

Suitability: Honours/Master by Research Doctorate

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Jemma Evans, Professor Lois Salamonsen**

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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 which are important for maternal fetal communication.

89. Defining uterine receptivity for embryo implantation

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Professor Lois Salamonsen, Dr Tracey Edgell, Dr Jemma Evans**
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tracey.edgell@hudson.org.au
jemma.evans@hudson.org.au

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.

90. The role of exosomal proteins in embryo implantation

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Prof Lois Salamonsen, Dr Hong Nguyen**
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hong.nguyen@hudson.org.au

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 characterized the proteome of endometrial exosomes and its changes across the menstrual cycle. This project aims to characterise the functional role of specific exosomal proteins in embryo implantation. Multiple cutting edge technologies including live cell imaging, cell transfection and, XCelligence, and a cell culture model of embryo implantation will be employed . 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.

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

Suitability: Honours/Master by Research Doctorate
Location: MHTP, MMC
Project Leaders: **Professor Kate Loveland, Helen Abud, Dr Julia Young**
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Project Description: Signalling through many distinct pathways drive normal testis development and are essential for normal fertility in males. Research projects are available examining the functions of activins, Wnts, Hedgehog and Snail proteins, using mouse models and human clinical materials. These projects examine how communication between the germ cells and their supporting somatic cells mediates normal spermatogenic progression (focussing on spermatogonial stem cells) and study how these signalling pathways may contribute to testicular cancer and infertility. Our culture models allow us to reveal how crosstalk between different signalling pathways governs the cellular processes that underpin fertility.

92. How does activin regulate Sertoli cell differentiation and function?

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Peter Stanton, A/Prof Craig Harrison**
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craig.harrison@hudson.org.au

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 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.

93. Male germ cells and the blood testis barrier

Suitability: Honours/Master by Research Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Peter Stanton, A/Prof Craig Harrison**
Email: *peter.stanton@hudson.org.au*
craig.harrison@hudson.org.au

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.

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

Suitability: Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **A/Prof Eva Dimitriadis, Dr Michelle van Sinderen**
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michelle.vansinderen@hudson.org.au

Project Description: Endometrial cancer is the most common gynaecological malignancy. Advanced disease has a very poor prognosis, current treatment options for advanced disease are inadequate so 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.

95. Nanoparticles targeting the uterus and placenta: utility in developing new contraceptives and treating pregnancy disorders

Suitability: Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **A/Prof Eva Dimitriadis, Dr Ellen Menkhorst, Dr Michelle van Sinderen**
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Project Description: Novel non-hormonal contraceptives that also block sexually transmitted infections (STIs) including HIV are urgently required. We have identified factors that may be targeted to prevent pregnancy via vaginal application. This project will investigate the combined administration of the contraceptive with anti-STI agents via nanoparticle delivery. Sustained release of the agents will be investigated *in vivo*. In addition we will investigate the use of nanoparticle delivery of agents to target the implantation site and the placenta to treat or prevent diseases associated with abnormal placentation.

96. Identification of testis-specific markers of male infertility

Suitability: Honours/Doctorate
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Peter Stanton, Professor Robert McLachlan**
Email: *peter.stanton@hudson.org.au*
robert.mclachlan@hudson.org.au

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 which surrounds testicular tubules where sperm are made contains numerous proteins which 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 protein labelling, MALDI-TOF ms/ms, SDS PAGE, western blotting, immunohistochemistry.

THE RITCHIE CENTRE

Monash University Departmental Heads:
Professor Euan Wallace, Department of Obstetrics and Gynaecology
Professor Nick Freezer, Department of Paediatrics

Centre Head:
Professor Stuart Hooper

The Ritchie Centre is Australia's premier clinical and research Centre for women, babies and children. The Ritchie Centre offers a unique setting where research advances can be rapidly applied for the benefit of women, seriously ill infants and children. This has led to rapid translation of its basic research into clinical trials and clinical practice. The Ritchie Centre is strategically located within the Monash Medical Centre. Integration into the daily life of the hospital means that its researchers are able to develop research in response to the complications that present in the clinical setting and demonstrate the value of bringing together a critical mass of dedicated scientists and clinicians to undertake translational research.

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

The Ritchie Centre has over 150 research staff and students, including fetal physiologists, sleep physiologists, immunologists, stem cell biologists, neonatologists, paediatricians, obstetricians, gynaecologists and radiologists.

Research Disciplines:
- Women's Health – Theme Leader A/Prof Caroline Gargett
- Fetal and Neonatal Health: respiratory and cardiovascular – Theme Leaders Professor Stuart Hooper and Associate Professor Tim Moss
- Fetal and Neonatal Health: brain injury and neurodevelopment – Theme Leader A/Prof David Walker
- Infant and Child Health – Theme Leaders Prof Rosemary Horne and Associate Professor Jim Buttery
- Cell Therapy and Regenerative Medicine – Theme Leaders Professor Graham Jenkin and Professor Euan Wallace

RESEARCH PROJECTS

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

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leaders: **A/Prof Caroline Gargett, Dr James Deane**
Email: *caroline.gargett@hudson.org.au*

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 cells 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.

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

Suitability: Honours
Location: Hudson Institute of Medical Research
Project Leaders: **A/Prof Caroline Gargett, Dr James Deane**
Email: *caroline.gargett@hudson.org.au*

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 if the precise perivascular locations of eMSC. Colocalisation with other stem cell markers (OCT4, SOX2, NANOG) and estrogen and progesterone receptors from normal and endometriosis women will also be examined. This project will generate beautiful images showing precisely where eMSC reside.

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

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr James Deane, Associate Professor Caroline Gargett**

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caroline.gargett@hudson.org.au

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 an 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.

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

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leader: A**ssociate Professor Caroline Gargett**

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Project Description: Recently it was discovered that an endometrial biopsy taken during the cycle before embryo transfer in *in vitro* fertilization (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.

101. How are endometrial stem cells regulated?

Suitability: Honours

Location: Hudson Institute of Medical Research

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

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caroline.gargett@hudson.org.au

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 signaling is a developmental pathway that is modulated during endometrial regeneration and over-activated in endometrial cancer. We have evidence that Hedgehog signaling 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 signaling in regulating endometrial stem cells.

102. Creatine and human pregnancy – it's time we knew more

Suitability: Honours, PhD

Location: Monash Medical Centre

Project Leaders: **Dr Hayley Dickinson, Dr Miranda Davies-Tuck, Professor Euan Wallace, Associate Professor David Walker**

Email: *hayley.dickinson@hudson.org.au*

Project Description: Creatine, in the form of energetically charged phosphocreatine, functions primarily as a phosphate donor for regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) in tissues of high and fluctuating energy demand. Most of our creatine is derived from eating animal protein (fish, meat) with less than half derived from endogenous synthesis. In our experiments we showed that the fetus relies upon the placental transfer of maternal creatine until late in pregnancy and that maternal supplementation with creatine in late pregnancy acts as an energy buffer to improve offspring survival and reduce morbidity from acute birth asphyxia. More recently, and most pertinent to our hypothesis that creatine may "rescue" and

protect the growth restricted fetus, we have shown that, compared to normal healthy pregnancies, maternal levels of creatine are significantly decreased in women with a small-for-gestational age baby.
This project will:

1. Define the normal range of creatine levels during pregnancy and the early postnatal period and correlate these with dietary intake of creatine
2. Determine whether higher levels of maternal creatine are associated with better pregnancy outcomes for the mother and baby

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

Suitability: Honours/PhD

Location: Monash Medical Centre

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

Email: *miranda.davies@hudson.org.au*

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 are available using routinely collected or recorded pregnancy and birth data as well as biological from the mother and baby at the birth.

104. Intrauterine growth restriction (IUGR) in the spiny mouse

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Hayley Dickinson, Dr Suzie Miller, Dr Mary Tolcos, Associate Professor David Walker**

Email: *hayley.dickinson@hudson.org.au*

Project Description: We have very recently developed a model of IUGR in the spiny mouse using a unique experimental approach. Our model is associated with asymmetric growth restriction, such that the growth of organs of high priority, such as the brain are preserved, whilst other organs, such as the kidney, are more severely affected, as is most commonly observed clinically. The aim of this project is to characterize the development of the organs systems (brain, heart, kidney, lung, adrenal gland, gonads) in these IUGR offspring. Once characterized, we will then use this model to test a range of therapeutic strategies to improve the growth of the fetus for improved postnatal outcomes.

105. Overcoming the 4-cell block in spiny mouse embryo culture

Suitability: Honours/PhD (project will be expanded for PhD)

Location: Monash Medical Centre

Project Leaders: **Dr Hayley Dickinson, Associate Professor David Walker**

Email: *hayley.dickinson@hudson.org.au*

Project Description: *In vivo*, the spiny mouse embryo cleaves at a similar rate to the human embryo, making it an ideal model to study human embryogenesis. In vitro, spiny mouse embryos readily cleave from the 1- to 4-cell stages and from the 8-cell stage through to blastocyst hatching. However, spiny mouse embryos will not cleave from 4- to 8-cells. We hypothesize, that this '4-cell block' coincides with embryonic genome activation (EGA) in this species. This project will determine when EGA occurs in the spiny mouse embryo, and develop culture conditions to support the development of spiny mouse embryos.

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

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Associate Professor David Walker, Dr Syed Baharom, Dr Suzie Miller, Dr Graeme Polglase**

Email: *david.walker@hudson.org.au*

Project Description: The aetiology of brain damage that manifests itself in some infants after 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.

107. Endothelial progenitor cells (epcs) in fetal blood and brain – role in repair and recovery from developmental brain injury

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Margie Castillo-Melendez, Dr Suzie Miller, Professor Graham Jenkin**

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Project Description: We hypothesize that EPCs from bone marrow are recruited in the developing brain following hypoxia and/or ischaemic (HI) injury, and determine the capacity of the fetal and newborn brain to limit and repair this damage caused by HI and inflammation. Specifically, we propose that EPCs are mobilized from fetal bone marrow following HI and limit brain damage by promoting vascularization of injured regions. EPCs derived from umbilical cord blood may be useful for therapeutic repair of brain injury in the postnatal brain following HI. By investigating preterm and term fetal sheep, we will provide new insights into the role of circulating EPCs in the developing brain under hypoxic conditions, explore the potential of circulating EPCs to serve as a prognostic marker of brain injury, and determine the therapeutic potential of EPCs for promoting recovery from perinatal brain injury.

108. Impact of dopamine in the immature brain

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Flora Wong, Associate Professor David Walker, Dr Suzie Miller**

Email: *flora.wong@hudson.org.au*

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 suggests 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.

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

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Flora Wong, Associate Professor David Walker**

Email: *flora.wong@hudson.org.au*

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 well-described in adults. However, little is known about neurovascular coupling in newborn babies. We aim to examine neurovascular coupling in the immature brain, using the lamb model. In fetal and newborn lambs, we will correlate changes in brain activity and brain blood flow. We will also assess how different drugs currently used in the neonatal intensive care unit on sick human babies would affect neurovascular coupling in the immature brain.

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

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr 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) alternatively 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 babies, by measuring brain oxygen at the babies' bedside with a spectrometer (Near infrared spectroscopy).

111. Use of activated protein c (Apc) to reduce brain injury from birth asphyxia

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Flora Wong, Associate Professor 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.

112. Novel treatments for preterm brain injury (1)

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Suzie Miller, Prof Graham Jenkin, Dr Margie Zakhem, Dr Tamara Yawno, Dr Beth Allison**

Email: *suzie.miller@hudson.org.au, graham.jenkin@hudson.org.au*

Project Description: In Australia, a baby is born with the brain injury that underlies cerebral palsy every 15 hours. Improvements in newborn care mean that most babies that are born preterm will survive, but prematurity remains linked to cerebral palsy. This project will examine whether melatonin, a free radical scavenger and steroid derived neuroprotectants can reduce brain damage caused by preterm lack of oxygen. Treatments will be administered to preterm (fetal) lambs following hypoxia in vitro.

113. Ganaxolone: a new treatment for neonatal seizures

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Tamara Yawno, Dr Suzie Miller, Dr Michael Fahey, Associate Professor 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 in term fetal sheep caused by hypoxia ischemia. This project will utilise our established fetal sheep model, with state-of-the-art monitoring equipment to investigate brain activity and brain histopathology.

114. Do cord blood stem cells reduce neonatal brain injury?

Suitability: Honours/PhD

Location: Hudson Institute & Monash Medical Centre

Project Leaders: **Dr Suzie Miller, Professor Graham Jenkin, Dr Tamara Yawno, Dr Courtney McDonald, Dr Margie Zakhem, Dr Michael Fahey, Dr Atul Malhotra**

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Project Description: 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 are undertaking projects that directly address the question of whether cord blood stem cells reduce perinatal brain injury, caused by conditions that include fetal growth restriction, premature birth or birth asphyxia, and the mechanisms by which the cells contained in cord blood offer protection to the brain and even regenerative potential. These projects utilise our established lamb model clinical conditions, with state-of-the-art neonatal care and magnetic resonance imaging to track the cells.

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

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Suzie Miller, Dr Tamara Yawno, Professor 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 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.

116. Progesterone treatment of the growth restricted fetus - a natural therapy

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Tamara Yawno, Dr Suzie Miller, A/Prof David Walker, 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 to pregnant sheep carrying either a well-grown or IUGR fetus and examine cerebral physiological and cellular responses, to correlate with neuropathology. In this study we will examine the potential of progesterone co-administered with betamethasone to protect the brain of IUGR fetuses and neonates.

117. Novel treatments for preeclampsia

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash University

Project Leaders: **Dr Rebecca Lim, Prof Euan Wallace**

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Project Description: Preeclampsia 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 preeclampsia. Resveratrol is becoming increasingly well known for its protective effects against cancer, cardiovascular disease, inflammation, obesity, age-related deteriorations and ischemic injuries, such as myocardial infarctions and stroke. Its potential as a therapeutic for preeclampsia is yet to be investigated in detail. Using a rat model of preeclampsia, we will determine the efficacy of resveratrol as a novel therapy. This project involves small animal surgery and molecular techniques.

118. 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

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Associate Professor Marcel Nold, Dr Claudia Nold**

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claudia.nold@hudson.org.au

Project Description: Direct clinical relevance: high Hands-on learning opportunities: Multi-color flow cytometry, protein arrays, cell culture of primary human blood cells. Surprisingly little is known about the immune and coagulation system of preterm infants, which therefore represent problematically blank pages for clinicians on the one hand, but a true frontier for researchers on the other. Another reason why preterm immunity and coagulation represent a new frontier is that technology has advanced enough only recently to allow us to extract large amounts of information from sample volumes as small as 0.5 ml - which in fact is a significant volume of blood to take from the tiny patients, considering that the total blood volume is as small as 35 ml in some of the babies. Our laboratory has obtained approval to conduct an exciting study in which blood is taken from extremely premature infants at 5 timepoints, thus allowing for a unique longitudinal view at 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. Since we also have access to the babies' clinical data, we will be able to perform correlation analyses and draw conclusions about the relevance of our findings to the major diseases of prematurity such as bronchopulmonary dysplasia, intracranial haemorrhage and necrotising enterocolitis. These insights may lead to the identification of biomarkers and/or new therapeutic targets, which are direly needed as several of these diseases are clinically highly problematic and currently untreatable.

119. Molecular tracking of the cytokine IL-37 in anti-inflammatory signalling

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Associate Professor Marcel Nold, Dr Claudia Nold, Dr Camden Lo**

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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.
The focus of this study is on elucidating the molecular mechanism of signalling cascades triggered by the anti-inflammatory cytokine interleukin 37 (IL-37). We have recently described IL-37's powerful beneficial effects, which endow this cytokine with a vast potential for therapeutic application. This project continues our research on IL-37 by 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, micrometer-scale resolution imaging as well as statistical analysis of the results.

120. 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

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Claudia Nold, A/Prof Marcel Nold, Associate Professor 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) of the preterm newborn causes considerable suffering for affected children and families and contributes substantially to health care costs. Necrotising enterocolitis (NEC) is a disease of the premature gut that is very poorly understood and that carries a high mortality. Importantly, no effective therapy is known for either of these devastating diseases. Neonatal immunity has been neglected by biomedical research; therefore, the immense importance of inflammation for BPD and NEC is only beginning to be recognised. In this study, we will assess the therapeutic potential of two innovative anti-inflammatory mediators, interleukin 1 receptor antagonist (IL-1Ra) and IL-37, in established animals models of BPD and NEC. A BPD-like lung disease will be triggered in newborn mice and we will investigate whether increased levels of IL-1Ra or IL-37 can protect the young mice from developing lung pathology. To assess such BPD-like pathology, we will analyse biochemical and cellular markers of inflammation as well as histological slides for alveolarisation and vascularisation on day 3 and 28 of life. To mimick NEC, newborn mice will not be allowed to breast-feed, but will be fed an equivalent to formula for 3 days. In addition, they will briefly be exposed to cold and hypoxia. The resulting pathology in the gut resembles human NEC, and again we will assess the protective properties of IL-1Ra and IL-37 on the cellular level by histology and flow cytometry and on the molecular level by analysis of various biochemical markers.

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

Suitability: Honours/PhD
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Claudia Nold, Dr Ina Rudloff, Associate Professor 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 received very little attention (not even 10 publications) in general and nothing at all was known about its function until 2010, when our group 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, including the mRNA and protein expression profile of IL-37 across a spectrum of cell types and the effect of IL-37 on an important molecular regulator of inflammation, the inflammasome.

122. The first in vivo exploration of IL-38

Suitability: Honours/PhD
Location: Hudson Institute of Medical Research
Project Leaders: **Dr Claudia Nold, Dr Ina Rudloff, Associate Professor Marcel Nold**

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Project Description: Direct clinical relevance: medium/low. 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, RNA detection by real-time PCR.
Like interleukin (IL)-37, IL-38 was discovered in silico in 2000, but received even less attention until our group renamed the new IL-1 family cytokines in 2010. There is some evidence that IL-38 has anti-inflammatory properties, but confirmation of the function of this cytokine is needed. We have generated the first IL-38 knockout mouse in the world and in this exciting project will undertake the first experiments that involve this mouse. In addition to employing the simple endotoxic shock model, we will study the effects of IL-38 in autoimmune disease.

123. Transition to life after birth

Suitability: Honours/PhD
Location: Monash Medical Centre
Project Leaders: **Professor Stuart Hooper, Dr Kelly Crossley, Dr Graeme Polglase, Dr Lauren Kerr**

Email: *stuart.hooper@hudson.org.au*

Project Description: The transition to life after birth is one of the greatest physiological challenges that humans face.

At birth, the airways are cleared of liquid, to allow the entry of air, which increases pulmonary blood flow and closes vascular shunts that by-pass the lungs during fetal life. Most infants smoothly make this transition, but many don't which can be life threatening and cause life-long problems. The aim of this project is to study the changes that occur at birth and to identify factors that both facilitate and impede these changes to reduce the risks that newborn infants face.

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

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: P**rofessor Stuart Hooper, Dr Lauren Kerr, Dr Marcus Kitchen (Physics)**

Email: *stuart.hooper@hudson.org.au*

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

125. Interrogating the NO pathway in the growth-restricted fetus?

Suitability: Honours

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Beth Allison, Dr 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 of 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 using an array of techniques including in vitro wire myopgraphy, real-time PCR, histology, immunohistochemistry and image analysis.

126. Preventing Lung Disease in Very Premature Babies

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Megan Wallace, Professor Stuart Hooper**

Email: *megan.wallace@hudson.org.au*

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.

127. Fetal lung growth and development

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leader: **Dr Megan Wallace, Dr Annie McDougall**

Email: *megan.wallace@hudson.org.au*

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.

128. The role of Trop2 in trophoblast invasion, placental development and preeclampsia

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leader: **Dr Megan Wallace, Associate Professor Evdokia Dimitriadis, Dr Annie McDougall**

Email: *megan.wallace@hudson.org.au*

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. Preeclampsia is a disease of pregnancy that is associated

with poor trophoblast invasion and inadequate remodeling of the spiral arteries; this leads to maternal systemic endothelial cell dysfunction, hypertension and proteinuria. If untreated, preeclampsia 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 suggests that its levels in the placenta are altered in preeclampsia. 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 preeclampsia. 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 preeclampsia and from gestational-age matched placentas.

129. Characterising the role of Trop2, in fetal development

Suitability: Honours

Location: Hudson Institute of Medical Research & Monash Medical Centre

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

Email: *megan.wallace@hudson.org.au*

Project Description: Trop2 is a protein that regulates cell proliferation and migration in tumours. 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 analyzing 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.

130. Amniotic Fluid Infection/Inflammation: Effects on Brain Development and Postnatal Behaviour

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Associate Professor Tim Moss, Dr Hayley Dickinson, Dr Mary Tolcos, Dr Graeme Polglase, Associate Professor David Walker**

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Project Description At present there is no clinically relevant animal model of amniotic fluid infection that allows investigation of the neurodevelopmental and postnatal behavioural outcomes. 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 determining 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 neurobehavior in spiny mice.

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

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Associate Professor Tim Moss, Dr Hayley Dickinson, Professor Euan Wallace**

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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 behavior, and may lead to disorders such as autism and schizophrenia: whether maternal immunization has this effect is unknown. This project is aimed at assessing the effects on brain development and postnatal behavior in spiny mice, after maternal immunization against whooping cough.

132. Early life immunisation and cardiovascular disease

Suitability: Honours

Location: Monash Medical Centre

Project Leaders: **Associate Professor Tim Moss, Professor 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 over-looked 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. In humans, mycobacterial infections, including tuberculosis, are associated with elevated rates of atherosclerosis. In rabbits fed a high fat diet, administration of the BCG vaccine against tuberculosis worsens atherosclerosis. A recent study in mice, however, suggests that early life BCG vaccination may protect against the development of atherosclerosis. The BCG vaccine is administered routinely worldwide to infants at risk of contracting tuberculosis. The effect of this procedure on development of atherosclerosis is unknown. While data from adult humans and rabbit experiments suggest that BCG vaccine might accelerate the progression of atherosclerosis, it is possible that administration early in life might be protective. The aim of this project is to determine the effect of BCG vaccination on the development of atherosclerosis in mice predisposed to development of vascular disease.

133. Improving the transition at birth in asphyxiated infants

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Graeme Polglase, Professor Stuart Hooper**

Email: *graeme.polglase@hudson.org.au*

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.

134. Protecting the brain from injury at preterm delivery

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Graeme Polglase, Dr Kelly Crossley**

Email: *graeme.polglase@hudson.org.au*
kelly.crossley@hudson.org.au

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 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.

135. How does the fetal cerebral cortex fold?

Suitability: Honours, PhD

Location: Monash Medical Centre

Project Leaders: **Dr Mary Tolcos, Associate Professor David Walker**

Email: *mary.tolcos@hudson.org.au*
david.walker@hudson.org.au

Project Description: The cerebral cortex is involved in high-level cognitive functions and intelligence. During normal brain development the growth of the cortex is accompanied by the onset of surface folding to produce sulci (grooves) and gyri (ridges). Brain folding is disturbed by premature birth, fetal hypoxia, and alcohol consumption during pregnancy but how these factors interfere with cortical development is unknown. This study will combine large animal surgery, immunohistochemistry, and nerve fibre tracing with MRI, to better understand cortical folding in the fetal brain following normal and abnormal pregnancies.

136. Effects of intrauterine growth restriction on cortical laminar development: Relevance to autism

Suitability: Honours

Location: Monash Medical Centre

Project Leader: **Dr Mary Tolcos**

Email: *mary.tolcos@hudson.org.au*

Project Description: Babies born intrauterine growth restricted (IUGR) have an increased risk of developing autism later in life. Recent evidence now suggests that cortical

layering is disrupted in autistic brains and that this accounts for abnormal functioning of the brain. It is also thought that these changes manifest in fetal life. We have a rodent model of IUGR, where the brain, although spared relative to other organs, is still retarded in growth and development. The aim of this project is to assess layering of the cerebral cortex in control and IUGR fetuses. This project will combine paraffin sectioning, histology, immunohistochemistry and image analysis.

137. Long-term effects of high dose caffeine treatment on the developing brain

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Mary Tolcos, Dr Robert De Matteo**

Email: *mary.tolcos@hudson.org.au*

Project Description: Babies born premature often develop apnoea of prematurity (AOP), a condition where breathing ceases for up to 20 seconds. AOP is treated with caffeine, however if apnoea continues, clinicians will often use higher doses. Clinical trials using high doses of caffeine in babies have now reported an increased incidence of cerebellar hemorrhage in babies and our animal experiments also indicate adverse effects on brain development in fetal sheep. We do not yet know whether these adverse outcomes resolve or increase over time. This project will use a fetal ovine model to determine the long-term impact of high dose caffeine exposure on the brain and cerebellum. This project will combine brain histology, immunohistochemistry, image analysis, immunofluorescence, and confocal microscopy.

138. Cerebellar development following chronic fetal hypoxia: Is vitamin C neuroprotective?

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Mary Tolcos, Dr Beth Allison, Professor Dino Giussani (Cambridge)**

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Project Description: Lack of oxygen to the fetal brain during pregnancy is one of the main causes of brain injury in newborns. Some of these infants will suffer neurodevelopmental and behavioural problems including decreased intelligence and cognition, learning difficulties, poor memory and attention deficits. It is likely that these deficits are associated with neuronal alterations in the cerebellum. This project will investigate the effect of fetal hypoxia on cerebellar development and the neuroprotective potential of antenatal vitamin C (an anti-oxidant), using an array of techniques including brain histology, immunohistochemistry, image analysis, immunofluorescence, and confocal microscopy.

The project will involve collaboration with Prof Dino Giussani and colleagues from Cambridge University.

139. Using a novel thyroid hormone analogue for the treatment of brain injury in intrauterine growth restriction

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Mary Tolcos, A/Prof David Walker, Dr Flora Wong**

Email: *mary.tolcos@hudson.org.au*

Project Description: Growth-restricted babies are often born with damaged brains, including injury to the white matter and cerebellum, and they often develop learning and behavioural problems, and even cerebral palsy. With no treatment for brain injury, our challenge is to develop safe and effective therapies. We will test a novel thyroid hormone analogue as an antenatal therapy in an animal model of fetal growth restriction, to provide the essential information for a clinical drug trial with growth-restricted human infants. This project combines small animal surgery, brain histology, immunohistochemistry, western blot analysis and qPCR.

140. Can creatine prevent neurological deficits at birth following in utero hypoxia in fetal and neonatal sheep?

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **A/Prof David Walker, Dr Hayley Dickinson, Dr Rob De Matteo**

Email: *david.walker@hudson.org.au*

Project Description: We have shown that maternally administered creatine protects the rodent brain from the effects of oxygen deprivation at the time of birth. Using pregnant sheep, we will now explore the possibility that creatine given over 20-25 days before natural term in sheep, is protective against the effects of brief, but severe in utero hypoxia. In this study we will extend previous experiments that showed neurological deficits in lambs born after in utero hypoxia 7-10 days before birth. We have developed a video-based scoring system for evaluating neonatal behavior from the moment of birth, and these new experiments will determine if prenatal creatine treatment can prevent or ameliorate the deficits we have previously documented. The clinical relevance of this project is that antenatal hypoxic events are thought to cause damage to the developing brain that is later expressed as cerebral palsy-like conditions in the newborn. Currently there are few, if any, treatments that can be given during pregnancy to prevent such outcomes. This project will establish if creatine is effective in protecting the developing brain against such insults.

141. Does placental insufficiency affect expression of creatine synthesizing enzymes and the creatine transporter-1 (CrT1)?

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Padma Murthi, Associate Professor David Walker, Dr Hayley Dickinson, Dr Stacey Ellery**

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Project Description: Placental compromise is present in several obstetric conditions that lead to poor fetal growth, preterm labor, and increased neonatal morbidity. These include preeclampsia, gestational diabetes, restricted placental growth, and abnormal regulation of amniotic fluid (poly/oligohydramnios). We have identified an important role for creatine in fetal development and fetal-neonatal transition at birth, and also that the placenta may be a key organ in both the synthesis and transport of creatine for the fetus. In this project we will determine if placental insufficiency is associated with alterations of creatine pathways using qPCR, immunoblotting, and immunocytochemistry techniques.

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

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Rob Bischof, Associate Professor Tim Moss, Dr Megan Wallace**

Email: *rob.bischof@hudson.org.au*
tim.moss@hudson.org.au

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, cell and molecular biology.

143. Long-term consequences of intrauterine growth restriction on cardiovascular control and function

Suitability: Honours

Location: Monash Medical Centre

Project Leaders: **Dr Stephanie Yiallourou, Professor Rosemary Horne**

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rosemary.horne@hudson.org.au

Project Description: Fetal growth restriction (FGR) occurs in approximately 10% of pregnancies and is associated with increased risk of prematurity and neurodevelopmental delay. Severe FGR usually results due to placental insufficiency, which compromises the delivery of oxygen and essential nutrients to the developing fetus. In utero, the FGR fetus alters sleep state distribution to preserve energy and once born these infants have delays in circadian rhythm maturation. Currently, few studies have investigated the long-term consequences of FGR on sleep and its architecture. Given that sleep is important for neurodevelopment and that poor sleep can lead to impairments in neurocognition, this study aims to assess the effect of FGR on sleep architecture in infants and children. To achieve these aims, this study involves analysis of brain wave activity recorded during a polysomnography study (sleep study).

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

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Associate Professor Gillian Nixon, Professor Rosemary Horne**

Email: *gillian.nixon@monashhealth.org*

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 finalizing development of a clinical scoring tool that will help predict children at highest risk of OSA without the need for polysomnography. In 2015 we will be testing the new tool for usability and accuracy. Is it helpful for GPs, ENT surgeons and paediatricians at the coal face?

145. Understanding the relationship between childhood obesity and obstructive sleep apnoea

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Professor Rosemary Horne, Associate Professor Gillian Nixon, Dr Lisa Walter**

Email: *rosemary.horne@hudson.org.au*

Project Description: Childhood obesity is reaching epidemic proportions in Western societies, with 1 in 4 Australian children being either overweight or obese. While obesity is well recognised as the primary cause of obstructive sleep apnoea (OSA) in adults, the relationship between the two disorders is less straightforward in childhood. In children, airway obstruction results primarily from enlarged adenoids and tonsils. With the rise in childhood obesity, however, more children are being seen clinically in whom obesity could significantly contribute to OSA, but the extent of this contribution is unclear. This study will answer important clinical questions. Does the added burden of OSA worsen any existing adverse cardiovascular or psychological outcomes in children with obesity? What factors are associated with a higher risk of OSA in obese children? The study involves polysomnography and MRI in obese and control children.

146. Sleep in children with cancer

Suitability: Honours/PhD

Location: Monash Medical Centre

Project Leaders: **Dr Lisa Walter, Prof Rosemary Horne**

Email: *lisa.walter@hudson.org.au*

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, and yet current research investigating the prevention and treatment of sleep disorders in children with cancer is sadly lacking. This study will examine sleep in children with cancer during the year following completion of treatment, utilizing actigraphy and validated questionnaires to provide a sound basis for clinical intervention to improve the quality of life of these children.

147. The effect of sleeping position on sleep disordered breathing severity and cardiovascular outcomes in children with sleep disordered breathing

Suitability: Honours

Location: Monash Medical Centre

Project Leaders: **Dr Lisa Walter, Prof Rosemary Horne**

Email: *lisa.walter@hudson.org.au*

Project Description: Sleep disordered breathing (SDB), a very common condition in children, has been associated with adverse cardiovascular outcomes such as elevated blood pressure and decreased baroreflex sensitivity. It has been identified in adults that sleeping in the supine position can increase the number of respiratory events that occur and worsen these cardiovascular outcomes. However, the etiology of SDB in adults is usually related to obesity, whereas in children SDB is more commonly associated with enlarged tonsils and adenoids. It remains unclear how sleeping position affects children, both in terms of disease severity and cardiovascular outcomes. This study will examine the effect of position on respiratory events, blood pressure and measures of autonomic function in children with SDB. The student will be involved in conducting sleep studies (polysomnography) and analysis of cardiovascular data.

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

Suitability: Honours

Location: Monash Medical Centre

Project Leaders: **Dr Lisa Walter, Prof Rosemary Horne**

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

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

Suitability: PhD

Location: Monash Medical Centre

Project Leaders: **Dr Sarah Biggs, Prof Rosemary Horne**

Email: *sarah.biggs@hudson.org.au*

Project Description : Children with primary snoring (PS) represent the greatest proportion of children with 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 which 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.

150. Preterm Infants in the NICU – Mechanisms of oxygen desaturations

Suitability: Honours/PhD

Location: Monash Medical Centre & Monash Newborn

Project Leaders: **Dr Kenneth Tan, Dr Atul Malhotra, Associate Professor Philip Berger**

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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. This project will involve physiological measurements of infants receiving respiratory support 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.

151. SYNTRACK: Linking ED data to detect outbreaks and vaccine safety signals

Suitability: Honours/BMedSci/PhD

Location: Monash Medical Centre

Project Leaders: **Associate Professor Jim Buttery, Associate Professor Franz Babl, Dr Simon Craig**

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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 3 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.

152. SNOTWATCH: Real time seasonal viral information for health providers

Suitability: BMedSci

Location: Monash Medical Centre

Project Leaders: **Associate Professor Jim Buttery, Dr Andrew Daley**

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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.

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

Suitability: BMedSci

Location: Monash Medical Centre

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

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nigel.crawford@rch.org.au

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, minimizing harm to the public.

154. Is creatine deficiency in preterm infants contributing to poor neurological outcomes?

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Newborn

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

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Project Description: Creatine, in the form of energetically charged phosphocreatine, functions as a phosphate donor for regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) in all cells. Low cerebral creatine is associated with significant intellectual disability and behavioural disorders. When the human fetus/newborn develops the capacity to produce creatine is unknown. Animal studies suggest that the capacity to de novo synthesise creatine occurs very late in gestation (0.9). The human placenta is capable of producing large amounts of creatine and creatine levels are higher during pregnancy in women, suggesting that the human fetus relies on maternal/placental supplies of creatine during pregnancy. There is recent clinical data to suggest that the preterm infant may become creatine deficient. This project will monitor creatine levels in preterm infants and determine the relationship between brain and peripheral creatine levels and neurological outcomes.

155. Cell based therapy for the ex-vivo reconditioning of donor lungs prior to lung transplantation Suitability: Suitability: Honours/PhD

Locations: Monash University, Hudson Institute of Medical Research and Newcastle University Medical School, Newcastle UK

Project Leaders: **Professor Graham Jenkin, Dr Rebecca Lim, Professor Andrew Fisher, Dr Lee Borthwick, Newcastle University UK.**

Email: *graham.jenkin@hudson.org.au*

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.

156. Novel treatments for preterm brain injury (2)

Suitability: Honours/PhD

Location: Hudson Institute of Medical & Monash Medical Centre

Project Leaders: **Dr Suzie Miller, Professor Graham Jenkin, Dr Zakhem Zakhem, Dr Tamara Yawno, Dr Beth Allison**

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graham.jenkin@hudson.org.au

Project Description: In Australia, a baby is born with the brain injury that underlies cerebral palsy every 15 hours. Improvements in newborn care mean that most babies that are born preterm will survive, but prematurity remains linked to cerebral palsy. Although umbilical cord blood derived stem cells are being used to treat cerebral palsy, there is currently insufficient evidence that such treatment will improve the underlying brain injury. This project will examine whether melatonin, a free radical scavenger, steroid derived neuroprotectants and/or umbilical cord blood stem cells can

reduce brain damage caused by preterm lack of oxygen. Treatments will be administered to preterm (fetal) lambs following hypoxia. The active constituents of cord blood will also be investigated *in vivo* and *in vitro*.

157. The effects of human amnion epithelial cells (haecs) following fetal inflammation

Suitability: Honours

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Beth Allison, Dr Tamara Yawno, Dr Suzie Miller, Dr Rebecca Lim**

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Project Description: Intrauterine inflammation is recognized 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, LPS) in preterm fetal sheep. This project will utilize techniques to investigate lung injury, such as lung histology, inflammatory assays, rtPCR, western blotting and stem cell tracking.

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

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Courtney McDonald, Professor Graham Jenkin, Dr George Thouas**

Email: *graham.jenkin@hudson.org.au*

Project Description: Umbilical cord blood and the umbilical cord are a recognised source of mesenchymal stem cells and the cord is lined by amnion epithelial cells, which have the potential to differentiate into a wide range of cell types and are also potently 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.

159. Tracking stem cells in vivo in regenerative medicine

Suitability: Honours

Location: Monash Biomedical Imaging & Hudson Institute of Medical Research

Project Leaders: **Dr Courtney McDonald, Professor Graham Jenkin, Dr Tony Goldschlager**

Email: *graham.jenkin@hudson.org.au*

Project Description: We are exploring the use of human amnion epithelial cells (hAECs), Mesenchymal Stromal Cells and Mesenchymal Progenitor Cells (MPCs) 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.

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

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Abhilasha Tiwari, Professor Graham Jenkin, Dr Courtney McDonald, Dr George Thouas, Associate Professor Mark Kirkland (Deakin University)**

Email: *graham.jenkin@hudson.org.au*

Project Description: Umbilical cord blood (UCB) is one of the richest sources of “young” hematopoietic stem cells. Currently, more than 3000 UCB stem cell transplants are performed each year. However, these are mostly restricted to children, as UCB samples usually do not contain sufficient stem cells to treat adults. The umbilical cord and cord blood also contains multiple potentially efficacious cell types for a range of diseases. Hence, this research project aims to develop and refine methods for expanding the number of stem cells obtained from human UCB and umbilical cord under laboratory conditions and translation of this research to the clinic. This stem cell research could help save lives of people suffering from blood disorders, cancers and auto-immune diseases. The experiments will include cell culture and molecular biology techniques and transplantation of UCB stem cells to mice to determine their efficacy.

161. Treatment of cystic fibrosis with stem cells

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **Dr Rebecca Lim, Professor Euan Wallace, Professor Graham Jenkin**

Email: *rebecca.lim@hudson.org.au*

Project Description: There is a dire need for a cell type therapy to replace dysfunctional lung epithelial cells in patients with cystic fibrosis. We aim to produce functional lung epithelial cells from placental stem cells or by iPS derived cells using synthetic mRNA technology. We will utilize a novel method of delivering these cells into the lungs of mouse or sheep models of cystic fibrosis to incorporating the functional lung epithelial cells into the respiratory conducting airway and the lung. We will track placental stem cell-derived lung epithelial cells in the lung using novel Imaging techniques and assess their effectiveness in repairing lung function of mice with cystic fibrosis.

162. Human amnion epithelial cells as therapy for lung inflammation in preterm newborns

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research

Project Leaders: **A/ProfTim Moss, Prof Graham Jenkin, Dr Rebecca Lim, Prof Euan Wallace**

Email: *graham.jenkin@hudson.org.au*

Project Description: Bronchopulmonary dysplasia (BPD) is a life-threatening chronic lung disease that affects many infants born very preterm. Lung inflammation likely underlies the pathogenesis of BPD. Epithelial cells isolated from the amniotic membrane 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 amnion epithelial cells on inflammatory responses of newborn preterm lambs. The experiments include whole-animal physiology, immunology, microscopy and molecular biology techniques.

163. Isolation and banking of placental tissues for future clinical therapies

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Professor Graham Jenkin, Dr Courtney McDonald, Dr George Thouas**

Email: *graham.jenkin@hudson.org.au*

Project Description: The umbilical cord is a recognised source of Mesenchymal Stem Cells and is lined by Amnion Epithelial Cells, which have the potential to differentiate into a wide range of cell types and are also potently immunomodulatory and anti-inflammatory. The use of these cells are being explored in a number of therapeutic settings. This project, carried out in collaboration with Cell Care, will validate method for collection, processing, 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.

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

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash Medical Centre

Project Leaders: **Dr Courtney McDonald, Dr Suzie Miller, Professor Graham Jenkin**

Email: *courtney.mcdonald@hudson.org.au*

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 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 multicolour flow cytometry to examine the mechanisms by which stem cells reduce perinatal brain injury.

165. Stem cells and tissue scaffolds

Suitability: Honours/PhD

Location: Monash Medical Centre & Hudson Institute of Medical Research

Project Leaders: **Dr Tony Goldschlager, Professor Graham Jenkin**

Email: *graham.jenkin@hudson.org.au*

Project Description: In these studies, we are investigating the suitability of novel new 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.

166. Tracking human stem cells in vivo in regenerative medicine

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Professor Graham Jenkin, Professor Euan Wallace, Dr Rebecca Lim, Dr Courtney McDonald**

Email: *graham.jenkin@hudson.org.au*

Project Description: We are exploring the use of human amnion epithelial cells (hAECs) and Mesenchymal Progenitor Cells (MPCs) as cellular regenerative therapy for a variety of diseases including bronchopulmonary dysplasia and chronic lung disease of the preterm infant and spinal disc repair. This project will utilise novel labeling techniques that will allow us to track the migration profile of stem cells in real-time.

167. Stem cells and pregnancy: What women want

Suitability: Honours

Location: Monash Medical Centre

Project Leaders: **Professor Euan Wallace, Professor Graham Jenkin**

Email: *graham.jenkin@hudson.org.au*

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.

168. A model of viral illness in pregnancy in the spiny mouse: the possible prenatal origin of mental illness?

Suitability: Honours

Location: Hudson Institute of Medical Research

Project Leaders: **Associate Professor David Walker, Dr Hayley Dickinson, Dr Udani Ratnayake (Florey)**

Email: *david.walker@hudson.org.au*
udani.ratnayake@monash.edu

Project Description: While the etiology of mental illnesses such as schizophrenia and autism remains unknown, many epidemiological and animal studies have identified a potential neurodevelopmental origin of these disorders. Our animal model, the precocial spiny mouse (Acomys cahirinus), is developmentally more advanced by term than conventional rodents, having largely completed organogenesis, and they are capable of coordinated motor activity and thermoregulation. The aim of this study is to determine if offspring born to pregnant spiny mice that are exposed to a prenatal infection show behavioural abnormalities which are comparable to symptoms of mental illness disorders such as schizophrenia and autism, as measured by a comprehensive battery of behavioural tests.

169. Activating the stem cell niche

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash University

Project Leaders: **Dr Rebecca Lim, Prof Euan Wallace**

Email: *rebecca.lim@hudson.org.au*

Project Description: Amnion stem cells have reparative potential in the lung. It is yet unknown how the amnion cells trigger the regenerative process to improve lung function. We will use an animal model to mimic bronchopulmonary dysplasia 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. Understanding the stem cell sheddome

Suitability: Honours/PhD

Location: Hudson Institute of Medical Research & Monash University

Project Leader: **Dr Rebecca Lim**

Email: *rebecca.lim@hudson.org.au*

Project Description: Exosomes are nano-sized particles shed by cells. They contain bioactive cargo such as microRNAs and proteins, which can exert effects on specific tissues and cell types. This project looks to characterise the exosomes released by amnion stem cells 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, tissue culture, electron microscopy, molecular biology, real-time PCR and western blotting.

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

Suitability: Honours/PhD

Location: Monash Medical Centre & Hudson Institute of Medical Research

Project Leaders: **Dr Rob Bischof, Associate Professor Tim Moss, Professor Euan Wallace**

Email: *rob.bischof@hudson.org.au*
tim.moss@hudson.org.au

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.

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/**

- NOTES -

- NOTES -

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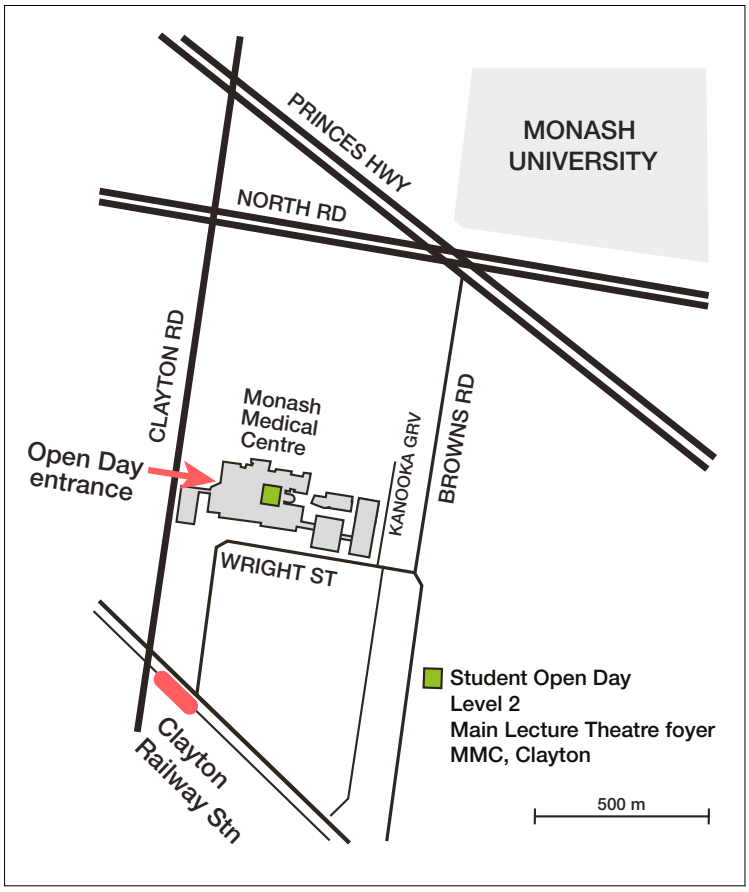

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