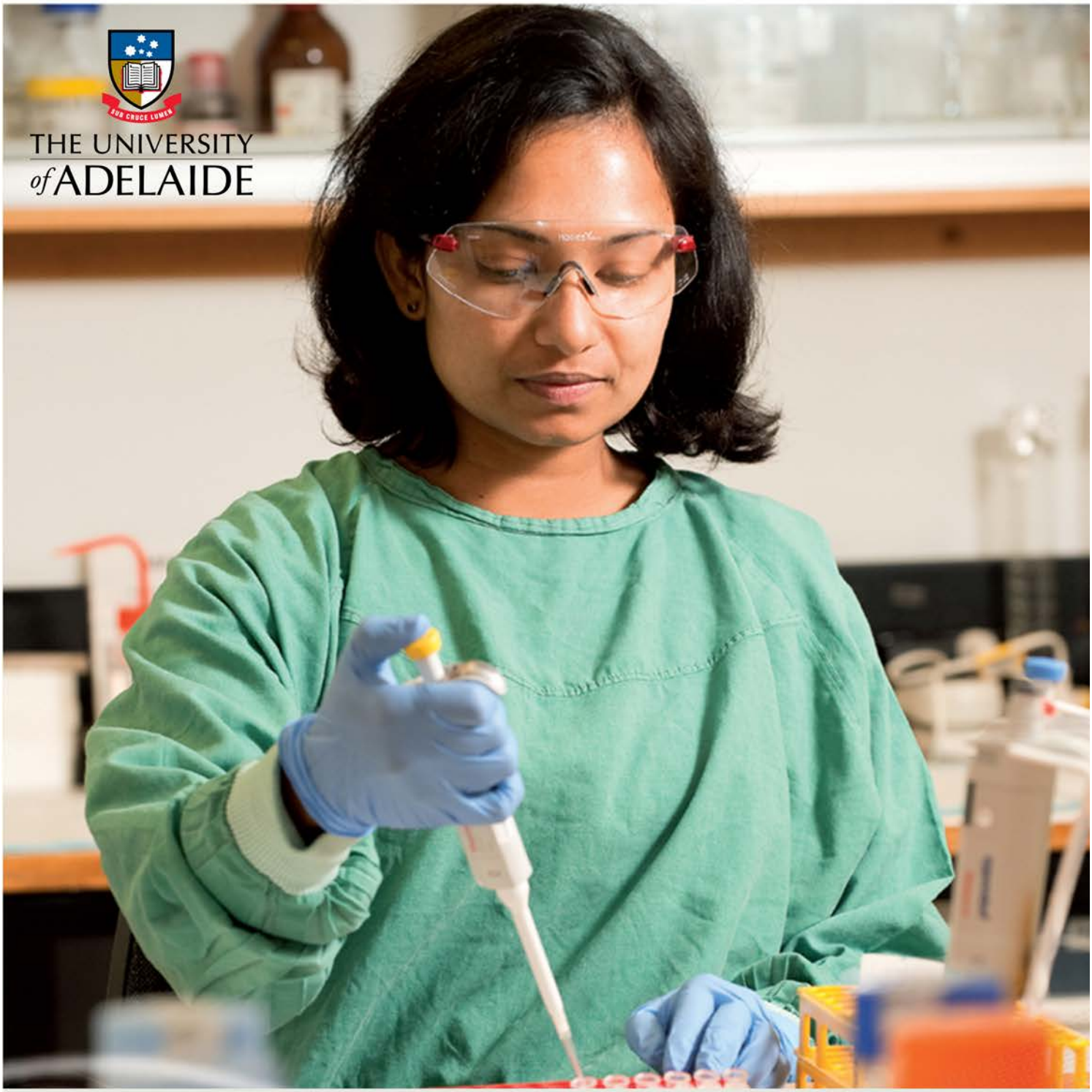


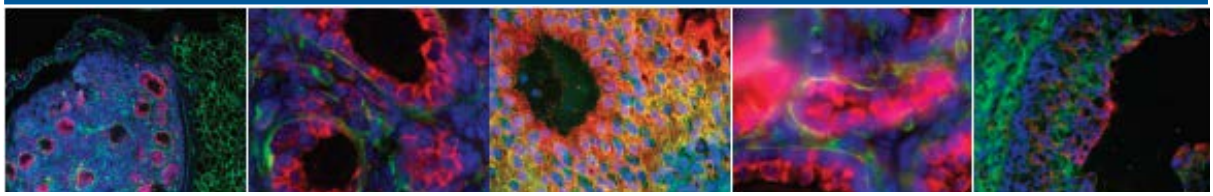
Discipline of Paediatrics & Discipline of Obstetrics and Gynaecology 2016 Honours Research Opportunities

Paediatrics and Child Health, Reproductive Biology and Regenerative Medicine

Research opportunities for Honours students in 2016

International Research Leaders in Reproductive Biology & Health, Paediatrics & Child Health and Regenerative Medicine

Last updated 12 August 2015



Contents

Make a difference

The Disciplines of Obstetrics and Gynaecology and Paediatrics invite you to join us for Honours.

Our Disciplines and its members have international reputations as research leaders in reproductive biology and medicine, maternal, fetal and child health, and reproductive and regenerative medicine. We are recognised for our strong links between cutting-edge discoveries in basic research with bridges through to clinical application and evaluation in evidence-based medicine. Our two Disciplines; Obstetrics & Gynaecology and Paediatrics include 170 staff and postgraduate students and over 300 clinical affiliates making us one of the largest and most productive paediatrics and reproductive health departments in the world. You have the chance to work, be educated and graduate from an internationally renowned area to the benefit of your future career.

Our two disciplines: Paediatrics, and Obstetrics and Gynaecology form part of the School of Medicine. We are closely associated with one research institute, the Robinson Research Institute, grouping together researchers with a focus on 4 major themes of research:

- Fertility and Conception
- Pregnancy and birth
- Early Origins of Health, and
- Child and Adolescent Health

Our major locations are in the Medical School, Women's and Children's Hospital, Lyell McEwin Hospital and Robinson Research Institute on King William Street, North Adelaide. Students can also study with our affiliates at these locations and others including the CSIRO and Flinders Medical Centre.

We are extremely research-active, with major project funding from the National Health & Medical Research Council, Australian Research Council and the National Institute of Health (US) amongst others. We host a number of NHMRC Senior Fellows, ARC Future Fellows and numerous Career Development and Training Fellows. Members of our Disciplines published over 400 peer-reviewed articles in 2014 in the top journals in their fields, including *Nature, the Cochrane Database of Systemic Reviews*, *Endocrine Reviews*, *Journal of Clinical Endocrinology & Metabolism*, *Journal of Paediatrics & Child Health*, *Lancet*, *Nature Genetics*, *New England Journal of Medicine*, *Obstetrics & Gynaecology* and *Theriogenology*.

This booklet contains information about our Honours course, enrolment and available scholarships, as well as a listing of the Honours research projects we are offering for study. Please remember that the research groups within the Disciplines and its affiliates may also have additional projects available, and often projects can be adapted to suit the interests and skills of the student. You should use the outlines in this book as a starting point in developing *your* project with a supervisor.

We invite you to join us for Honours and develop your future career.

Eligibility and study options

Students who have completed an undergraduate degree in a science course, for example B Science, B Health Science, or B Animal Science, or who have completed 3 years or more of the MBBS program, are invited to apply for Honours positions within our Discipline. To be eligible for Honours, a candidate must have completed the requirements for a Bachelor degree or equivalent to a standard that is acceptable to the Faculty for the purposes of admission into the Honours program. For more information please visit:

http://health.adelaide.edu.au/future-students/honours/

A credit average within relevant subjects is the usual standard expected, but students with a strong interest in a particular field and the support of their proposed supervisor/s are also encouraged to apply, and often find their Honours year very stimulating and successful.

Honours students are invited to enrol either full-time (1 year of study), or part-time and study over two/three years. The main Honours intake is in February, and students may also commence mid-year.

Facilities and training opportunities

Honours students have access to the core facilities of the University, Disciplines and Robinson Research Institute as required for their specific projects. These include state-of-the-art molecular biology and imaging equipment, confocal microscopes, large and small animal surgeries and *in vivo* facilities, cell culture laboratories and an embryology laboratory. Some projects have strong clinical components with patient involvement, epidemiological

methodologies and genomic linkage. Of course, Honours students will also get in depth training in their research field and its techniques within their research group throughout their research projects.

Our Honours program

Our program is designed for you to develop specific knowledge and skills in your chosen research field as well as general skills for working independently, critical reasoning, scientific writing and presentation. Our Honours students each undertake a full-year research project (or part-time equivalent), with the majority of assessments structured around this. In addition, our Honours structured program teaches students the skills they need to succeed in research, including experimental design and statistics, research ethics, an understanding of the scientific method, good record keeping and laboratory practice, literature searching and bibliographic software and critical evaluation of literature during "journal club" tutorial discussions. The overall objective of the program is for students to demonstrate a deep understanding and interpretation of their subject area and have the ability to clearly and thoroughly present the project.

Aims of the Honours Program:

- To provide mentored training and education in scientific research methods.
- To develop skills for independent critical thought and learning.
- To develop logical reasoning and written and oral presentation skills.
- To encourage interest in a broad range of child health and reproduction related science.

One on one contact with the supervisor and other members of the research team is the main method by which students gain these skills during Honours. In addition, hands on experience, communication with other members of the Honours class, the Honours coordinator, and the School is invaluable.

Assessment

The Honours program consists of two graded courses:

Research Skills – Semester 1

Research Project – Semester 1 and 2

Research Skills requires students to participate in tutored discussion on the philosophical, ethical, methodological and procedural considerations of laboratory and clinical based medical science. Articles are selected and presented by the students in "Journal Club" literature reading and evaluation sessions. Comprehension and capacity to critique literature will be assessed during a 3 hour critical literature exercise. Student's knowledge of material presented in the tutorial series is assessed by written examination.

The Research Project consists of one full-time academic year of research (or part-time equivalent) on a defined project under the supervision of a designated supervisor(s). This culminates with the preparation by the candidate of a thesis, written in the form of a scientific paper, describing the conduct and outcomes of the research project.

A critical review of relevant literature that supports the rationale behind the research is also submitted for assessment.

In addition, students give three seminars during the year:

- An introduction/research proposal
- A progress seminar
- A final seminar, or thesis defence, after thesis submission

Honours graduate career pathways

Our previous Honours students have gone on to successful careers in a wide range of roles. The skill base that Honours gives you is essential for those wanting to undertake postgraduate research training and education, and valuable across a wide range of areas. Approximately half of our students go on to further study, including PhD and postgraduate Medicine. Others are now employed as research assistants and officers, journal editors, science communicators and investment managers.

Interested?

What to do next:

1. **Browse** this booklet to determine a research area or project that interests you.

2. **Discuss** potential projects with Supervisors at our annual Honours Information Session in August or contact them directly using the information provided in this booklet.

If you have any questions about your eligibility, part-time study or other queries, you should contact:

Dr Kathy Gatford
Honours Coordinator
Phone: (08) 8313 4158
Email: kathy.gatford@adelaide.edu.au

3. **Complete** the 'Expression of interest in Honours' form on the following page.

4. You will be **notified** via email of the outcome of your application by the Discipline Honours Coordinator following the release of any outstanding results. If your application is accepted you will receive an acceptance letter with enrolment forms.

You will be able to enrol once enrolments open (usually late January for Semester 1 or late July for Semester 2).
For more information regarding the enrolment process contact:

Faculty of Health Sciences
Plaza Building, Level 2
North Terrace Campus
(08) 8313 5336

Or visit the Faculty of Health Sciences website:

http://health.adelaide.edu.au/future-students/honours/

Expression of Interest in an Honours Project

Personal Details					
Student ID		Name			
Address				Postcode	
Phone		Email			

Alternate contact details (if we need to contact you at a different place/number/ e-mail):					
Dates to use alternate contact details		Start date		End date	
Address				Country	
Telephone		Email			

Candidature Details			
Undergraduate degree			
Citizenship (Tick one)	☐ Australian citizen ☐ New Zealand citizen ☐ permanent resident	☐ I will hold a visa whilst studying honours (international students) Visa type:	
Start date (Year/Semester)	20	☐ Semester 1	☐ Semester 2
Enrolment load	☐ Full time	☐ Part time	

Honours Project Details		
Title		
Discipline (Tick one)	☐ Paediatrics	☐ Obstetrics & Gynaecology

Supervision details			
Primary Supervisor		Location	
Email		Phone	
Signature		Date	
Cosupervisor		Email	

ATTACH a copy of your current academic transcript when you return this form. If you have completed undergraduate studies at an institution other than the University of Adelaide you will also need to provide an official copy of your transcript once your final marks are available.

DUE DATE: 6 November for first round Semester 1 offers of the following year.
17 June for mid-year offers (Semester 2 of the same year).

Forms will still be accepted after these dates but will be treated on an *ad hoc* basis.

SUBMIT via: Email: sprh.l_and_t@adelaide.edu.au
In person/ by post to: Honours Coordinator, Discipline of Obstetrics and Gynaecology, Level 3, Medical School South, Frome Road, University of Adelaide, Adelaide SA 5005.

Honours Scholarships and Support

Scholarships are available to support full time Honours study.

Eligibility for scholarships

Applicants must:

- be enrolled in their Honours degree full time.
- be Australian citizens, permanent residents of Australia or hold a suitable Visa.
- have completed an undergraduate degree in a relevant area before scholarship commencement.
- meet the specific requirements for eligibility for specific scholarships (see below).

Honours scholarship conditions:

The following conditions apply to all Honours scholarships awarded through our School:

1. The award of the scholarship is subject to acceptance into an Honours program at the University of Adelaide through either the Discipline of Obstetrics and Gynaecology or Discipline of Paediatrics and commencement of the project within 12 months of approval.
2. Awardees may only hold one Honours scholarship funded from within The University of Adelaide.
3. The awardee must complete their Honours degree. Should the awardee withdraw from the Honours program the scholarship will be cancelled and all scholarship monies are repayable to the sponsor (i.e. Discipline of O & G, Robinson Research Institute or Project supervisor).
4. You must notify the project sponsor in writing if you:
    a. discontinue your studies
    b. cease to study or cease to be enrolled
    c. change your course of study
    d. change your address

Selection

The Scholarships selection committee will review applications, considering the following:
eligibility criteria

- student Grade Point Average (GPA)
- the strength of the potential Honours project
- endorsement from the potential supervisor
- The selection committee may choose not to award scholarships based on the quality of applications.

2015 Jeffrey Robinson Honours Scholarship recipient, Cassandra Carbone.

Discipline Honours Scholarships

Honours scholarships are available for Honours students enrolled through either of our Disciplines. Each scholarship will be valued at $4000 pa, of which the student will receive $3,000 (one instalment in each semester). The remaining $1,000 will be allocated to the research area supervising the student as a contribution to the costs of the project. These scholarships will be awarded to students who have a Distinction average in their previous undergraduate studies and who enrol in Honours in either the Discipline of Paediatrics or Obstetrics and Gynaecology.

Robinson Research Institute Honours Scholarship

The Robinson Research Institute (RRI) is internationally recognised for excellence in research in the field of reproductive, pregnancy and child health. We focus on the early stages of life to improve the health and well-being of children and families over the life course and across generations, in Australia and around the world.

Our four Themes – Fertility and Conception, Pregnancy and Birth, Early Origins of Health, and Child and Adolescent Health, bring together large teams of researchers working on related areas to stimulate scientific collaboration and find answers to global research priorities and health problems that affect children and families across generations and global communities.

2016 Jeffrey Robinson Honours Scholarship

The purpose of The Jeffrey Robinson Honours Scholarship is to attract high quality students to contribute to the Themes and Research Priorities of the Institute. Emeritus Professor Jeffrey Robinson, born in Northern Ireland, was appointed Professor of Obstetrics and Gynaecology at the University of Adelaide in 1986. Under his leadership the University developed its outstanding reputation for research into fetal-maternal physiology and reproductive medicine and biology. In 2006 he was awarded a Commander of the British Empire (CBE) for his services to maternal and fetal heath. Jeffrey continues to be involved in research at the Institute.

The Robinson Research Institute will award one Jeffery Robinson Honours Scholarship in 2016 to an exceptional student. The successful applicant will:

- Undertake a full-time Honours research project directly aligned to a RRI Research priority (http://www.adelaide.edu.au/robinson-research-institute/research/priorities/)
- Be supervised by a member of the Robinson Research Institute
- Be selected based on academic merit. Academic merit will be determined by students' cumulative Grade Point Averages (GPAs) for their undergraduate degree

The total value of the scholarship is $4,000 of which the student will receive $3,000 (one instalment in each semester). The remaining $1,000 will be allocated to the research department supervising the student as a contribution to the costs of the project.

To be eligible for a Robinson Research Institute Honours Scholarship, the primary supervisor of the project must be a member of the institute. Please confirm this with your proposed supervisor prior to applying.

Scholarship Application Form

APPLICANT DETAILS		
First name:	Surname:	Student no:
Undergraduate Degree:	Institution:	
Postal Address:		
Citizenship: (please circle) Australian citizen New Zealand citizen Permanent Resident Visa Holder		
Email:	Phone:	Mobile:

PROJECT DETAILS
Proposed Honours Project Title:
Brief Description: (250 word maximum)

PRIMARY SUPERVISOR	
Email:	Phone:
Location:	
Signature:	Date:
Co-supervisor:	Signature:

Scholarship/s being applied for: (Please tick appropriate box/es)

☐ Robinson Research Institute (my Primary supervisor is a member of the institute).

☐ Discipline Scholarship

Please explain how this research project aligns to the Discipline, Robinson Research Institute or Research Centre strategic research objectives. (250 word maximum).

Declaration

I declare to the best of my knowledge and belief that the information I have supplied in this application is correct and complete.
I understand that selection for these Honours scholarships is competitive and not all applicants who meet the basic eligibility criteria are necessarily awarded scholarships. I have read and understand the conditions of these scholarships as outlined in the 'Honours Research Opportunities booklet'. I recognise that it is my responsibility to provide all necessary documentation and applications with incomplete documentation cannot be considered.
I understand my photo may be used for marketing purposes related to the award of this scholarship.

Applicant signature:

Date:

ATTACH to this application:

1. A cover letter.
2. Your 'Expression of interest in Honours' form and transcript.
3. A one page current CV.

DUE DATE: 6 November, 2015.

SUBMIT via: Email: sprh.l_and_t@adelaide.edu.au

OR

In person/ by post to: Honours Coordinator
Dr Kathy Gatford
Level 3, Medical School South, Frome Road
University of Adelaide, Adelaide SA 5005

Discipline of Obstetrics and Gynaecology

- Medical School
- Women's and Children's Hospital
- The Robinson Research Institute
- Lyell McEwin Hospital

"The Discipline of Obstetrics and Gynaecology is a leading centre of academic research with an international reputation in the areas of maternal-fetal physiology, reproductive immunology, embryology, advanced reproductive technology, feto-maternal medicine, the fetal origins of adult disease, perinatology, placentology, the genomics of pregnancy disorders e.g. preterm delivery, regenerative medicine and stem cell research, pre-eclampsia and cerebral palsy, urogynaecology and postmenopausal health . We are the largest and most research-active Discipline of Obstetrics and Gynaecology in the world and our range of interests from basic science through to clinical practice creates multiple and successful career paths for our graduates."

A/Professor Paul Duggan
Head of Discipline of Obstetrics and Gynaecology

Cerebral Palsy Research Group


Supervisors (photographs left to right)
Emeritus Professor Alastair MacLennan
Dr Clare Van Eyk

Location: Women's and Children's Hospital

PROJECT : Cerebral Palsy - Is it in your genes? Understanding the causes of the cerebral palsies.

Supervisors/Contact Persons:
Emeritus Professor Alastair MacLennan
alastair.maclennan@adelaide.edu.au
Dr Clare van Eyk
clare.vaneyk@adelaide.edu.au

Project Background/Aims

Cerebral palsy (CP) is heterogeneous with different clinical types, co-morbidities, brain imaging patterns, causes and now also heterogeneous underlying genetic variants. Few are solely due to severe hypoxia or ischaemia at birth. This common myth has held back research in causation. The cost of litigation has devastating effects on maternity services with unnecessarily high cesarean delivery rates and subsequent maternal morbidity and mortality. CP rates have remained the same for 50 years despite a sixfold increase in cesarean birth. Epidemiological studies have shown that the origins of most CP are prior to labour. Increased risk is associated with preterm delivery, congenital malformations, intrauterine infection, fetal growth restriction, multiple pregnancy and placental abnormalities. Hypoxia at birth may be primary or secondary to pre-existing pathology and international criteria help to separate the few cases of CP due to acute intrapartum hypoxia.

Until recently 1-2% of CP (mostly familial) had been linked to causative mutations. Recent genetic studies of sporadic CP cases using new generation exome sequencing show that 14% of cases have likely causative single gene mutations and up to 31% have clinically relevant copy number variations. The genetic variants are heterogeneous and require function investigations in silico and in animal models to prove causation. Current Honours projects involve validation of cerebral palsy candidate genes in zebrafish motility models. Whole genome sequencing, fine scale copy number variant investigations and gene expression studies are likely to extend the percentage of cases with a genetic pathway. Clinical risk factors could act as triggers for CP where there is genetic susceptibility. These new findings should refocus research about the causes of these complex and varied neurodevelopmental disorders.

References

MacLennan AH, Thompson SC, Gecz J. Cerebral Palsy – Causes, pathways, and the role of genetic variants. Amer J Obstet Gynecol, 2015; DOI: 10.1016/j.ajog.2015.05.034

McMichael G, Bainbridge MN, Haan E, Corbett M, Gardner A, Thompson SC et al. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. Mol Psychiatr 2015; Feb 10. doi: 10.1038/mp.2014.189.

McMichael G, Girirajan S, Moreno-De-Luca A, Gecz J, Shard C, Nguyen LS et al. Rare Copy Number Variation in Cerebral Palsy. Eur J Hum Genet 2013;22:40-45

Developmental Biology of the Ovary

Supervisors

Professor Ray Rodgers
Dr Katja Hummitzsch
Dr Helen Irving Rodgers

Location: Level 2, Medical School North

Contact Person
Professor Ray Rodgers
Phone: 8313 3932
ray.rodgers@adelaide.edu.au

The ovary produces eggs and hormones, and these functions are dependent upon growth and development of follicles and corpora lutea within the ovary. Control of these processes is externally via hormones, or internally by growth factors and the extracellular matrix. In particular our laboratory focuses on the role of extracellular matrix in regulating ovarian function as this has previously been poorly investigated. We use molecular and cellular biology approaches. This area is important as extracellular matrix can be used to regulate ovarian cell function in vitro, as well as aiding in the understanding of normal reproductive function and ovarian diseases including infertility and hormone imbalances.

Project: Generation of reactive oxygen species and the regulation of the antioxidant GPX1 in granulosa cells

Supervisors
Ray Rodgers
Katja Hummitzsch
Helen Irving-Rodgers
Hugh Harris, Chemistry, University of Adelaide

Project Background

In a collaboration examining trace elements in ovaries using the Australian Synchrotron we recently found that selenium accumulates in granulosa cells as ovarian follicles approach ovulation (1). We identified the selenoprotein as glutathione peroxidase 1 (GPX1) and found that its expression was higher in the cumulus cells associated with oocytes that resulted in a successfully pregnancy. GPX1 acts an antioxidant protecting cells against oxidant damage. The regulation of GPX1 in the follicle is unknown. We hypothesise that GPX1 expression is driven by production of reactive oxygen species, and in particular those generated by cytochrome P450 enzymes involved in production of estradiol.

This project will examine the above hypothesis using bovine granulosa cells. Cells will be cultured and steroid hormone production induced in immature cells and conversely inhibited in mature cells and the effects on reactive oxygen species and GPX1 expression examined. The cells will be obtained from ovaries that we collect from an abattoir. This project will provide valuable information on the role of selenium and antioxidant proteins in follicle function.

References

1. Ceko MJ, Hummitzsch K, Hatzirodos N, Bonner W, James SA, Kirby JK, Russell DL, Lane M, Rodgers RJ, Harris HH (2015) X-Ray Fluorescence imaging and other analyses identify selenium and GPX1 as important in female reproductive function Metallomics 2015, 7, 66-77

Project: Fetal testis formation

Supervisors
Ray Rodgers
Katja Hummitzsch
Helen Irving-Rodgers

Project Background

Most studies of testis formation focus on the genes involved in sex determination, testis cord formation or spermatogenesis. Less is understood about the origins of Sertoli and Leydig cells which are supposedly the counterparts to granulosa and thecal cells of the ovarian follicle and it is believed that Sertoli and granulosa cells originate from the same precursor (1).

Recently we published new findings about the origin of granulosa cells during fetal ovary development which were contrary to established theories. We believe that precursor cell (GREL cell) gives rise to ovarian surface epithelial cells or granulosa cells depending on contact with germ cells (2). Following our hypothesis, it is unlikely that Sertoli cells originate from the same precursor as granulosa cells because in contrast to the ovary, a simple surface epithelium and tunica albuginea are established very early in testis formation.

To identify the possible origin of the somatic cells of the bovine testis, fetal testes from different

developmental stages will be collected from an abattoir, histological processed, stained for somatic and germ cell markers as well as extracellular matrix markers and examined by fluorescence microscopy.

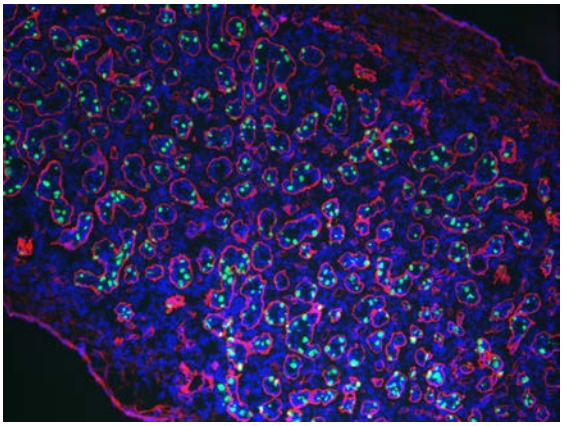


Figure 1: Bovine fetal testis stained for germ cell marker OCT3/4 (green) and

References:

1. Albrecht KH and Eicher EM (2001) Evidence That *Sry* Is Expressed in Pre-Sertoli Cells and Sertoli and Granulosa Cells Have a Common Precursor. Dev Biol. 240: 92-107.
2. Hummitzsch K, Irving-Rodgers HF, Hatzirodos N, Bonner WM, Sabatier L, Reinhardt DP, Sado Y, Ninomiya Y, Wilhelm D, Rodgers RJ (2013) A new model of development of the mammalian ovary and follicles. *PLoS One*.;8(2):e55578. DOI: 10.1371/journal.pone.0055578.

Project: Regulation of atresia in the ovary by phospholipase A_2 and LPCAT3

Supervisors
Ray Rodgers
Helen Irving-Rodgers
Nic Hatzirodos

Project Background

Atresia is the regulated process of follicular destruction that ultimately controls the timing and number of follicles which will ovulate. Apoptotic cell death is a well-known mechanism of atresia. Using a metabolomic approach we recently identified altered phosphatidylcholine and fatty acid molecules in atretic follicles compared to healthy follicles (unpublished observations). Phospholipase A_2 (PLA_2) comprises a family of esterases that hydrolyze phospholipids to release free fatty acids and lysophospholipids. These esterases have been implicated in non-apoptotic cell death (1). Lysophosphatidylcholine acyltransferase 3 (LPCAT3) preforms the opposite reaction leading to the esterification of phosphatidylcholine (Fig. 1) and has also been shown to regulate cell death (2).

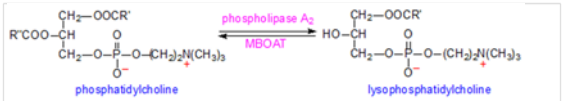


Figure 1. Regulation of phosphatidylcholine by PLA_2 and LPCAT3.

We hypothesis that PLA_2 and LPCAT3 are involved in the death of granulosa and theca cells during follicular atresia. Their involvement in these processes will be investigated using molecular and Western blot analyses of cells from healthy and atretic follicles. The regulation of these enzymes and other family members will be examined in granulosa and theca cells in vitro. This information is important to understand initiators of follicular atresia.

1. Shinzawa K and Tsujimoto Y (2003) PLA2 activity is required for nuclear shrinkage in caspase-independent cell death. Journal Cell Biology. 163: 1219-1230
2. Jain S, Zhang X, Khandelwal PJ, Saunders AJ, Cummings BS, Oelkers P (2009) J Lipid Res. 50: 1563-1570.

Early Development Group



Supervisors

Dr Hannah Brown
Dr Mel McDowall
Associate Professor Jeremy Thompson

Location: Medical School

Contact Persons
Dr Hannah Brown
8313 8175
hannah.brown@adelaide.edu.au

Dr Mel McDowell
ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP)
Robinson Research Institute
8313 1013
melanie.mcdowall@adelaide.edu.au

The Early Development Group comprises a team of excited and dedicated scientists working to understand the intricate requirements for the early embryo. We know that oocytes (eggs) and embryos are exquisitely sensitive to perturbations and stress during the earliest moments of life, and that just small challenges during this period (before embryo implantation, or first 4-5 days of life) can have dramatic, long-term health implications. These changes can be mediated through the health of your parents (diabetes, obesity) or in the laboratory during assisted reproductive technologies such as IVF (new culture systems and tests for embryo quality). We have experimental models for "improved" and "compromised" development and utilise both rodent and agricultural models to determine the how, what and whys of early embryo development.

Research Areas
We are interested in the **epigenetic status of the embryo** and how environmental challenges (both the health of parents and assisted reproduction technologies such as IVF) can alter that landscape. In regards to parental health, our primary focus is the impact of diabetes, but collaborating with a number of researchers with models of environmental stress (obesity, immune etc.). We also have models of improved oocyte and embryo development for use in IVF, such as specific growth factors (oocyte secreted factors) and systems to replace hormone hyperstimulation (in vitro oocyte maturation, IVM). We are particularly interested in the histone modification profile of the early embryo, and how this regulated gene expression, and the "program" of the early embryo.

The **metabolic profile** (how energy is made) can indicate if an oocyte/embryo is healthier, hence more likely to result in a successful pregnancy. Embryos produced in a lab (IVF, in vitro) have higher levels of metabolism than embryos produced within the body (in vivo) and why this happens is largely unknown. Furthermore, metabolism can be used as a non-invasive test for selecting the healthiest embryo. Our research group is part of the Centre for Nanoscale Biophotonics, and our collaborations with chemists and physicists have allowed us to develop and test new sensing technologies to learn more about the requirements for the embryo on the nano-scale.

The third is the **oxygen requirement of the oocyte**, and a novel, exciting role for haemoglobin, in oxygen balance in the follicle during the last stages of oocyte (egg) development. Very recently, we have identified a functional role for haemoglobin, once thought to be only present in red blood cells, but now described in a number of tissues, in the ovary. Through industry collaboration with Cook Medical, we continue to explore the role for haemoglobin in oocyte development, and the possibility that it regulated oxygen homeostasis in the follicle.

PROJECT: Is fresh best? Investigating the influence of vitrification (freezing) on embryo metabolism

Supervisors:
Melanie McDowall
A/Prof Jeremy Thompson
Dr Hayley McGrice

Project Background

The aim of this project is to evaluate if vitrification (embryo freezing) alters the metabolism of cattle embryos. Furthermore, if specific media additives can improve freeze/thaw outcomes.

In vitro embryo production (IVP) is a technology that is increasingly utilised in livestock farming as it allows for more rapid dissemination of valuable genetics compared to traditional husbandry techniques, such as artificial insemination. Vitrification (embryo freezing) is an essential part of IVP, allowing the storage and transportation of embryos. However, the effects of freezing on embryo metabolism are largely unknown.

Methodology

- Embryology (cattle)/cell culture
- Confocal microscopy

- Image analyses
- Molecular biology
- Metabolism assays

PROJECT: Is negative energy balance and high lipids during the peri-conception period contributing to subfertility in high performance dairy cattle?

Supervisors:
Melanie McDowall
A/Prof Jeremy Thompson
Dr Hayley McGrice

Project Background

The aim of this project is to investigate the relationship between high lipids (NEFAs) and low glucose environments during oocyte maturation. This will include the metabolism and signalling pathways.

Over the past two decades, there has been a steady decline in the fertility of the high performance dairy cattle (Holstein) worldwide. In Australia, the 1% decline in the in calf rate is costs the industry $5M annually. The final stages of oocyte growth and maturation coincide with peak lactation, a time when the cow is in negative energy balance and has a high NEFA, low glucose circulatory profile. We have demonstrated that oocytes exposed to high NEFAs have perturbed embryo development.

Methodology

- Embryology (cattle)/cell culture
- Confocal microscopy
- Molecular biology
- Metabolism assays

PROJECT: What makes and embryo quite? Turning the in vitro into the in vivo.

Supervisors:
Melanie McDowall
A/Prof Jeremy Thompson
Dr Karen Kind

Project Background

What makes an embryo quiet? A mixed bag of cells: what causes blastomeres within the same embryo to behave differently?

Embryos created in the lab (in vitro) utilise energy differently to embryos created within the body (in vivo). Indeed, the healthiest in vivo-derived embryos have a "quiet" metabolic profile. Furthermore, the healthiest embryos contain cells (blastomeres) with similar metabolic profiles. When stressed, blastomeres within the same embryo tend to have more metabolic variability or "heterogeneity". The degree of heterogeneity within an embryo can be used as a non-invasive test of embryo health.

Methodology

- Embryology (tissue culture)
- Protein biology (immunohistochemistry and Western blot)
- Molecular biology
- Confocal fluorescence microscopy

PROJECT: Making better embryos in the lab: the long-term effects of oocyte secreted factors.

Supervisors:
Melanie McDowall
A/Prof Jeremy Thompson
Lesley Ritter

Project Background

The aim of this project is to determine if different combinations of oocyte secreted factors improve embryo health.

IVF technologies have improved greatly since the first IVF baby was born almost 40 years old and this can largely be attributed to improved culture systems and techniques. Our group has developed a special culture system that more closely replicates what happens in the body, lending to improved pregnancies rates. However, the mechanisms and long-term consequences need to be determined.

Methodology

- Embryology (tissue culture)
- Molecular biology
- Protein biology (immunohistochemistry,Western blot)
- Confocal fluorescence microscopy

PROJECT: How Mum and Dad are compromising even before you're born! (How diabetes compromises eggs and sperm)

Project Background

It is very clear that diabetes (or hyperglycaemia) impacts both the oocyte (egg) and sperm in negative ways, and that some of these changes are to the offspring. We are identifying the molecular, epigenetic and signalling events resulting from long-term exposure to high glucose responsible for the increase change of negative health impacts in the next generation, including increased incidence of diabetes, obesity and other metabolic disorders.

Potential projects include:

Supervisor:
Hannah Brown

- **Understanding the impact of diabetes on the histone landscape of the early embryo**
- **Exploring new histone modifications in human sperm, particularly in diabetic dads**

Supervisor:
Melanie McDowall

- **Characterising the signalling pathways that are induced in eggs and embryos from diabetic mums (interactions between fat and sugar sensing pathways**

Projects are likely to include animal work (mouse), and will involve embryology, molecular biology and epigenetic analysis, protein biology (immunohistochemistry and Western blot) and confocal fluorescence microscopy.

PROJECT: A novel role for haemoglobin in oocyte oxygen homeostasis

Project Background

Recently we have identified a role for haemoglobin, the red blood cell oxygen carrying molecule, in oocyte development. Addition of haemoglobin to oocyte maturation protocols improves the blastocyst rate, however further research is required to identify the mechanism of action, as well as the safety and efficacy for embryo culture.

Potential projects include:

Supervisor:
Hannah Brown

- **Understanding the functional role for haemoglobin in oocyte maturation (including safety and efficacy) Exploring the role of haemoglobin in the placenta (in collaboration with Prof. Claire Roberts)**

Projects are likely to include animal work (mouse) and small animal surgeries, and will involve embryology, molecular biology, protein biology (immunohistochemistry and Western blot) and confocal fluorescence microscopy.molecular biology, plasmid preps, PCR, transfection of mammalian cells.

PROJECT: What are the epigenetic consequences of oocyte secreted factors?

Supervisor:
Hannah Brown

Project Background

IVF technologies have improved greatly since the first IVF baby was born almost 40 years old and this can largely be attributed to improved culture systems and techniques. Our group has developed a special culture system that more closely replicates what happens in the body, lending to improved pregnancies rates. However, the mechanisms and long-term consequences (including epigenetics programing) need to be determined

Projects are likely to include animal work (mouse) and small animal surgeries, and will involve embryology (tissue culture), molecular biology, protein biology (immunohistochemistry and Western blot) and confocal fluorescence microscopy.

References:

- Hyperglycaemic conditions perturb mouse oocyte in vitro developmental competence via beta-O-linked glycosylation of heat shock protein 90.
- Frank LA, Sutton-McDowall ML, Brown HM, Russell DL, Gilchrist RB, Thompson JG. Hum Reprod. 2014 Jun;29(6):1292-303.
- The effect of peri-conception hyperglycaemia and the involvement of the hexosamine biosynthesis pathway in mediating oocyte and embryo developmental competence. Frank LA, Sutton-McDowall ML, Gilchrist RB, Thompson JG. Mol Reprod Dev. 2014 May;81(5):391-408
- Oxygen-regulated gene expression in murine cumulus cells. Kind KL, Tam KK, Banwell KM, Gauld AD, Russell DL, Macpherson AM, Brown HM, Frank LA, Peet DJ, Thompson JG. Reprod Fertil Dev. 2014
- Altered pregnancy outcomes in mice following treatment with the hyperglycaemia mimetic, glucosamine, during the periconception period.
- Schelbach CJ, Robker RL, Bennett BD, Gauld AD, Thompson JG, Kind KL. Reprod Fertil Dev. 2013;25(2):405-16.
- Effect of varying glucose and glucosamine concentration in vitro on mouse oocyte maturation and developmental competence. Frank LA, Sutton-McDowall ML, Russell DL, Wang X, Feil DK, Gilchrist RB, Thompson JG. Reprod Fertil Dev. 2013;25(8):1095-104.
- Microarray analysis of mRNA from cumulus cells following in vivo or in vitro maturation of mouse cumulus-oocyte complexes. Kind KL, Banwell KM, Gebhardt KM, Macpherson A, Gauld A, Russell DL, Thompson JG. Reprod Fertil Dev. 2013;25(2):426-38
- Metabolic differences in bovine cumulus-oocyte complexes matured in vitro in the presence or absence of follicle-stimulating hormone and bone morphogenetic protein 15. Sutton-McDowall ML, Mottershead DG, Gardner DK, Gilchrist RB, Thompson JG. Biol Reprod. 2012 Oct 11;87(4):87.

Early Life Programming of Health and Disease



Supervisors

Professor Julie Owens
Dr Kathy Gatford
Emeritus Professor Jeffrey Robinson

Contact Persons:
Dr Kathy Gatford
8313 4158
kathy.gatford@adelaide.edu.au

Our research group are international leaders in the investigation of the intergenerational and perinatal origins of metabolic and cardiovascular health in postnatal life. We focus on how our health can be profoundly influenced by events in early life and possibly in previous generations, including diabetes, obesity and cardiovascular increasing risk of disease.
Common exposures in early life that affect our later health include placental and fetal growth restriction, maternal vitamin supplementation and maternal obesity and diabetes.

Our aims are to:

- understand how these exposures interact with the genome and affect the epigenome to determine our later health
- Identify interventions to either prevent these conditions that program later health or to overcome or reverse such programming.

Recent key discoveries include:

- placental restriction
    - inducing diabetes in adult offspring via impaired beta cell function and growth and insulin resistance
    - causing obesity in offspring via altered appetite control
- alter expression of novel small regulatory RNAs that target and repress expression of multiple mRNAs to affect major pathways and funtions
- maternal folate deficiency or folic acid supplementation changes the epigenome and physiology of offspring.

Our research strategies include:

- novel experimental models of common early life exposures in non human species
- pre-clinical evaluation of intervention strategies in non-human species
- clinical research in human cohorts with exposure to common pregnancy complications
- in vivo characterisation of insulin action, glucose and lipid control and other physiological functions
- metabolite and hormone analysis by enzymatic analysis and immunoassay
- quantitative morphmetric analysis of tissue structures underpinning function
- molecular analysis of expression of regulatory RNAs and protein coding genes and protein expression and activation by quantitative PCR, microarray and western immunoblotting
- analysis of epigenetic state of genes by bisulfite treatment of DNA and Sequenom or Pyrosequencing
- bioinformatics, including pathway analysis of array data of microRNA and mRNA expression.

We publish in the top discipline specific and general journals, are highly cited and regularly invite to speak at leading conferences. Our students publish their work, present at conferences and have gone on to a range of careers as researchers, academics, health professionals, in the biotechnology and pharmaceutical industry and management.

PROJECT: Does maternal obesity alter epigenetic state and expression of key regulatory and functional genes in offspring?

Supervisors
Prof Julie Owens
Dr Karen Kind
Prof Marie Dziadek

Project Background

Maternal obesity is common and increasing and results in a high birthweight and greater risk of obesity and diabetes in offspring later in life. This may be partly responsible for the growing epidemic in obesity, including in children. Maternal obesity exposes the developing fetus to high glucose and insulin abundance and other metabolic and endocrine changes when its epigenetic state is changing rapidly. This may alter DNA methylation, a major epigenetic mechanism that influences expression of genes. Once established, epigenetic patterns are heritable through cell division, and can persist long term. There is new evidence in humans that maternal obesity can change epigenetic state of some genes at birth in the new born, including that of PPARCG1A, an important regulator of many metabolic genes. This project will test for the first time using rodents, if maternal obesity alters epigenetic state and expression of PPARCG1A and other important genes in key metabolic tissues of offspring later in life. DNA methylation in the promoter region of PPARCG1A and other genes and their expression in liver and skeletal muscle of offspring of obese fat fed mothers will be analysed by pyrosequencing after DNA bisulfite treatment and by RTPCR. The outcomes will show if epigenetic modifications are a key part of the mechanism by which maternal obesity affects metabolic health of offspring and if these can be used as markers of this for future translation into human studies.

PROJECT: Growth hormone and pregnancy – a novel approach to increase fetal growth

Supervisors
Dr Kathy Gatford
Dr Beverly Muhlhausler
Prof Claire Roberts

ProjectBackground

Fetal growth is restricted in ~10% of pregnancies and there is currently no effective treatment to prevent this developing. We know that injecting pregnant animals with growth hormone can increase placental function and fetal growth. In this project we are investigating whether enhancing the mother's own growth hormone production can improve fetal growth, and investigating the role of the placenta in this effect. We are using pre-clinical models of normal and growth-restricted pregnancies in the mouse to test a novel dietary intervention, with the long-term aim of developing a safe dietary supplement that reduces the risk of IUGR in women who are identified as being "at risk". The student will gain an understanding of in utero growth, placental development and function, and growth hormone biology, and will gain skills in small animal in vivo studies (Aim 1), in vivo analysis of placental function using tracer uptake (Aim 2), and analysis of placental structure (Aim 3), data analysis, and written and oral presentation skills.

PROJECT: Does exercise have the same benefits if you grew poorly before birth?

Supervisors
Dr Kathy Gatford
Prof Glenn McConell (Victoria University)
Dr Karen Kind

ProjectBackground

Exercise improves responses to insulin and glucose control, including in type 2 diabetic subjects. In particular, exercise training increases muscle uptake of glucose in response to insulin, improving whole-body glucose control. We know that individuals who grew poorly before birth are at increased risk of diabetes, partly because they have reduced insulin sensitivity compared to individuals who were of normal size at birth. In this project, funded by Diabetes Australia Research Trust, we are currently exploring whether these growth-restricted individuals obtain the same improvement in insulin sensitivity and glucose control when they undergo exercise training compared to individuals of normal size at birth. We are using the placentally-restricted sheep, a pre-clinical large animal model of restricted growth in utero, allowing us to test causality and remove confounding due to variable post-natal environment and genetics. The longer-term aims are to develop specific guidelines for use of exercise as an intervention to prevent diabetes in those whose growth was restricted before birth. In this project, an Honours student will investigate underlying mechanisms for exercise training responses, including changes in expression of insulin signaling proteins, GLUT4 localisation and muscle fibre type. The student will gain an understanding of in utero growth, exercise physiology and insulin action and signalling, and will gain skills in immunohistochemistry, analysis of protein expression by Western blot protein, data analysis, and written and oral presentation skills.

References

- M Dziadek. 2005 Genomic imprinting and epigenetic programming of fetal development: In: Perinatal Programming: Early Life Determinants of Adult Health and Disease (Eds

DM Hodgson and C Coe). Taylor and Francis Medical Books, London.
- Gatford KL, Mohammad SN, Harland ML, De Blasio MJ, Fowden AL, Robinson JS, Owens JA (2008) Impaired beta-cell function and inadequate compensatory increases in beta-cell mass after intrauterine growth restriction in sheep. Endocrinology. Oct;149(10):5118-27.
- Quigley SP, Kleemann DO, Walker SK, Speck PA, Rudiger SR, Nattrass GS, DeBlasio MJ, Owens JA (2008) Effect of variable long-term maternal feed allowance on the development of the ovine placenta and fetus. Placenta. Jun;29(6):539-48.
- Owens JA, Gatford KL, De Blasio MJ, Edwards LJ, McMillen IC, Fowden AL (2007) Restriction of placental growth in sheep impairs insulin secretion but not sensitivity before birth. J Physiol. Nov 1;584(Pt 3):935-49.
- De Blasio MJ, Gatford KL, Harland ML, Robinson JS, and Owens JA. Placental restriction reduces insulin sensitivity and expression of insulin signaling and glucose transporter genes in skeletal muscle, but not liver, in young sheep. Endocrinology 153: 2142-2151, 2012.
- Gatford KL, Sulaiman SA, Mohammad SNB, De Blasio MJ, Harland ML, Simmons RA, and Owens JA. Neonatal exendin-4 treatment reduces growth, fat deposition and glucose tolerance during treatment in the intrauterine growth-restricted lamb. PLoS ONE 8: e56553, 2013.
- Pitcher JB, Schneider LA, Drysdale JL, Ridding MC, and Owens JA. Motor system development of the preterm and low birthweight infant. Clinics in Perinatology 38: 605-625, 2011
- Gatford KL*, Kaur G*, Falcao-Tebas F, Wadley GD, Wlodek ME, Laker RC, Ebeling PR, McConell GK 2014 Exercise as an intervention to improve metabolic outcomes after intrauterine growth restriction (review). American Journal of Physiology: Endocrinology and Metabolism 306(9):E999-E1012

Early Origins of Cancer

Supervisors

Dr Tina Bianco-Miotto
Professor Julie Owens
Professor Claire Roberts
Dr Carlos Marcelino Rodriguez López

Location: Medical School

Contact Person
Dr Tina Bianco-Miotto
tina.bianco@adelaide.edu.au

Increasing evidence suggests that maternal obesity which is often a result of a high fat diet, and a common cause of high birth weight, is a major risk factor for cancer in offspring. High birth weight is also predictive of child and adult obesity. Obesity is increasingly implicated in cancer and of concern, maternal obesity and the associated high birth weight is increasingly common suggesting the potential for a growing contribution to the burden of disease in future. Our research objective is to determine if the early life environment, such as maternal obesity and diet, promotes excessive growth before birth and acts on the breast or prostate during development leading to an increased susceptibility of the individual to breast or prostate cancer in later life. Given that obesity is a growing epidemic world-wide, understanding how obesity can influence the development and progression of cancer may provide opportunities for implementing preventative and therapeutic strategies. We are also investigating whether epigenetic mechanisms are involved in the developmental origins of cancer. Epigenetic mechanisms include DNA methylation, histone modification and microRNAs and alter gene expression but unlike DNA mutations do not alter the DNA sequence. These epigenetic changes are targets for therapy and intervention due to their reversibility.

PROJECT: Is a high fat diet early in life associated with an increased risk of cancer in adult offspring?

Project Background

Using animal models we will investigate whether the offspring of mothers on a high fat diet are at an increased risk of developing cancer. The rat or mouse prostate or mammary glands from maternal high fat and control diets will be examined for histological abnormalities. Key markers of cancer development, cell proliferation and apoptosis will be assessed by immunohistochemistry and real time quantitative PCR (qPCR). To investigate which molecular determinants are altered between the diet groups, the expression of key epigenetic modifications will be assessed by qPCR, immunohistochemistry, high resolution melting, methylation specific PCR, and pyrosequencing. MicroRNA expression will be assessed by qPCR. Well-characterised mouse models of prostate or breast cancer will also be utilised to test dietary interventions.

PROJECT: Epigenetic biomarkers in prostate cancer

Project Background

Prostate cancer is the most prevalent cancer (29% of all cancer cases diagnosed in men) and is the second-leading cause of cancer death (Australian Institute Health and Welfare). The majority of men diagnosed with prostate cancer have insignificant disease that will not cause death. With current tests, it is not possible to differentiate between men with insignificant cancer and those who have clinically significant and life-threatening prostate cancer. We and others have shown that epigenetic modifications play a major role in prostate carcinogenesis, are capable of differentiating between benign and malignant disease, and are useful markers of response to therapy. Our aim is to identify epigenetic gene signatures of prostate cancer that discriminate aggressive disease from clinically insignificant disease. In the process we will also identify novel therapeutic and diagnostic markers; and so provide a powerful tool for the more effective clinical management of prostate cancer. The techniques used will include nucleic acid extraction from prostate tissue samples and blood samples, culturing

prostate cancer cells and tissues, qPCR or immunohistochemistry for the assessment of DNA methylation or microRNA markers. This is a project that will utilise cellular and molecular biology techniques and will suit students interested in learning bioinformatic analyses.

PROJECT: Correlation of tissue specific somatic mutations leading to cancer and tissue specific DNA methylation

Project Background

Distinct tissue-specific patterns of DNA methylation have been identified in multicellular organisms (1,2). In humans, tissue-specific differentially methylated regions (TS-DMRs) have been mapped for almost 20 different tissues and cell types (1,2). Although DNA methylation is a key element in the regulation of cellular phenotypes across tissues (2), the presence of this DNA modification increases the rate at methylated cytosines due to the frequent deamination of methylated cytosine to thymine. When these substitutions occur in germ cells, they constitute a heritable mutation that may eventually rise to polymorphic frequencies (3). Conversely, when these mutations occur on somatic cells they do not translate into heritable variability but can lead to tissue specific genetic diseases such as cancer. The aim of this project is to exploit current human databases and assess the effect of tissue specific DNA methylation on the generation of somatic mutations leading to cancer in humans. This project will ideally suit an enthusiastic student who is interested in learning more about epigenetic mechanisms in humans as well as learning more about bioinformatics and computational biology. A g

Techniques/Skills Learnt:

- Database mining
- Whole genome/methylome cross-referencing and analysis computational approaches
- DNA methylation analysis skills and an introduction into the epigenetics field
- Good knowledge of computer systems is essential

References

- Florian Eckhart et al., 2006. DNA methylation profiling of human chromosomes 6, 20 and 22. Nature Genetics.
- Ryan Lister et al., 2009. Human DNA methylomes at base resolution show widespread epigenomic differences. Nature.
- Hehuang Xie et al., 2009. SNP-based prediction of the human germ cell methylation landscape. Genomics.

Evidence Based Women's Health Care

Supervisor and Contact Person
Professor Ben Mol
Phone: 0434 122170
ben.mol@adelaide.edu.au

Location: Women's and Children's hospital

It is our vision that each medical intervention in reproductive health care must have an underlying evidence base demonstrating that the action is expected to do more good than harm. In case of uncertainty, patients must be informed on the evidence gap, and optimally, be offered participation in a randomized controlled trial (RCT).

Our mission is to create evidence on the effectiveness of all medical interventions in reproductive health care, preferably through large collaborations in randomised clinical trials (RCTs), to provide insight in the available evidence tailored to the individual patient for both patients and doctors.

The way to achieve these aims goes along three dimensions:

- Create large datasets
- National and International collaboration
- Involve young people

In view of the latter aim, we are particularly motivated to involve young people in the process of evidence based medicine, including evidence generation, evidence synthesis, clinical guidelines and implementation. I have an international orientation and we therefore stimulate students to work abroad. For an Honours project, this implicates that part of it can be done in Europe (London, Amsterdam or other cities), North America (Vancouver, Toronto, Chicago, Galveston, Salt Lake City, New York), Auckland or in Ho-Chi-Minh City (Vietnam), Sao Paulo (Brasil) or Rosario (Argentina).

We are also very keen that students present their results at national and international scientific meetings. A meeting abstract is often a very good opportunity to wrap-up preliminary results. Many of my students have presented their work at national and international meetings, and it is always the intention to do so.

PROJECT: Induction of labour in South Australia.

Project Background/Aims

Induction of labour is one of the most common obstetric interventions. In South Australia in 2011, 31% of women had labour induced [1]. The main indications for induction of labour were prolonged pregnancy (18%), hypertensive disorders (14%), diabetes or gestational diabetes (8.0%), poor fetal growth and premature rupture of membranes (7%). Fifty-one percent of inductions of labour were performed for other than defined indications [1]. Cervical ripening is required in more than half of cases [1].

Indications for IOL include but are not limited to: suspected IUGR, suspected LGA, Hypertensive disorders of pregnancy, maternal BMI, maternal age, diabetes, cholestasis and, decreasingly, social induction. While international evidence advocates induction of labour for many indications and suggests that this does not increase the caesarian section rate – there are many differences in our patient population, our burden of disease, our definition of disease and therefore indication for induction (for example no proteinuria is required to diagnose preeclampsia) and, potentially, our practice around induction of labour.

We regularly audit our LSCS practice and note that the rate of LSCS for a primip who is induced is up to 60%, while our LSCS rate typically reflects the national average at ~31%.

We aim to audit practice and outcomes around induction of labour at the Lyell McEwin and the WCH.

References

[1] South Australian perinatal outcome data 2011. http://www.sahealth.sa.gov.au/wps/wcm/connect/71a4600041ffdcb9957dbdf8b1e08c6d/13103.1-Pregnancy+Outcomes+Report-FINAL.pdf?MOD=AJPERES&CACHEID=71a4600041ffdcb9957dbdf8b1e08c6d

PROJECT: Treatment and outcomes in subfertile couples in South Australia.

Project Background/Aims

Subfertility, defined as failure to achieve pregnancy after one year of unprotected intercourse, affects more than 70 million couples worldwide, and over 40 million of these couples seek fertility care.1,2 When

unresolved, it is considered one of life's great catastrophes. Subfertility has a negative role not only on emotional wellbeing of women, their partners and families, but also on the whole society. Infertility treatment may be a great burden for couples, not only financial, but also emotional, leading to distress, depression and discontinuation of treatment. In the last three decades, assisted reproductive technology (ART) has allowed many couples to have a healthy baby.1

To cut expenses for couples on infertility treatment, the government covers the financial costs of treatment by full or partial reimbursement of treatment cycles which, however increases the financial costs of healthcare and affects all taxpayers. It is without question that in some cases delays in treatment thus allowing a longer period for pregnancy to occur naturally. However, delay of treatment also may decrease its effectiveness of treatment, but, on the other hand, complicated medical tests and useless treatment procedures could have a negative impact on psychological state, leading to discontinuation of infertility treatment and thus in turn also impacting the outcomes of treatment. Thus, in summary, a key issues in optimizing the success of subfertility treatment is to define optimal balance between expectant management and clinical treatment, thus combining optimal effectiveness.

Methods: We plan a retrospective observational cohort study in subfertile couples in South Australia, in which we will study subfertile couples who sought treatment in fertility clinics of South Australia between January and December 2012. Primary outcome will be time to conception resulting in ongoing pregnancy. Secondary outcomes will be cumulative pregnancy rates per couple in ART methods (ovulation induction, IUI, IVF/ICSI) as well as cumulative life birth rates. Miscarriage, pregnancy complications among which stillbirth, preterm birth, preeclampsia, gestational diabetes, subfertility cause and treatment methods will be also registered.

We aim to collect data on 1,000 couples. Demographic characteristics (couple's age, hormonal levels, semen parameters) and subfertility-related characteristics (duration of subfertility and type of subfertility) will be used to describe groups of subfertile patients. We will estimate time to ongoing pregnancy using Kaplan-Meier analysis and Cox regression. For percentages 95% confidence intervals (95% CI) will be applied. The student will be involved in data-collection, analysis, interpretation and report of the results.

References

- Steures P, van der Steeg JW, Hompes PG, Habbema JD, Eijkemans MJ, Broekmans FJ, et al. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. Lancet 2006 Jul 15;368:216-21.
- Brandes M, Hamilton CJ, de Bruin JP, Nelen WL, Kremer JA. The relative contribution of IVF to the total ongoing pregnancy rate in a subfertile cohort. Hum Reprod 2010 Jan;25:118-2

Fertility and Conception




Supervisors (photographs left to right)
Dr Lisa Moran
Philippa Middleton
Professor Ben Mol
Professor Robert Norman

Location: Women's and Children's Hospital

PROJECT: The effect of nutrition and exercise pre-conception in males and females on fertility, fetal and neonatal outcomes: A systematic review, meta-analysis and research translation.

Supervisors

Dr Lisa Moran
Philippa Middleton
Prof Ben Mol

Contact Person
Dr Lisa Moran
Phone: 8313 1352
lisa.moran@adelaide.edu.au
http://www.adelaide.edu.au/directory/lisa.moran

Project Background/Aims

The nutritional and exercise status of the parents has potential important influences on fertility, achieving a healthy pregnancy and live birth and optimising the health of offspring. This includes factors such as optimising diet quality, micronutrient intake and obesity status in both the mother and father. However, there is a lack of evidence-based guidelines or assessment of the quality of the existing research to inform optimal medical and allied health practice to optimise nutritional and exercise status. This project will involve a systematic review of the research literature on the effect of nutritional (micronutrient, macronutrient, energy, diet quality, food groups, consistency with population recommendations) and exercise status and interventions modulating nutritional and exercise status (including weight loss) preconception on fertility, pregnancy outcomes and offspring health. It will then involve translation of this research to health professional and consumer education resources.

References

- Paediatr Perinat Epidemiol. 2012 Jul;26 Suppl 1:285-301. doi: 10.1111/j.1365-3016.2012.01281.x. Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. Ramakrishnan U, Grant F, Goldenberg T, Zongrone A, Martorell R.

PROJECT: Weight management in polycystic ovary syndrome

Supervisors

Dr Lisa Moran
Professor Robert Norman

Contact Person
Dr Lisa Moran
Phone: 8313 1352
lisa.moran@adelaide.edu.au
http://www.adelaide.edu.au/directory/lisa.moran

Project Background/Aims

Up to half of Australian reproductive-aged women are overweight or obese, with weight-associated risks of infertility and adverse effects on the health of the offspring. Overweight and obesity significantly worsen the reproductive, metabolic and psychological implications of polycystic ovary syndrome (PCOS) – a serious endocrine condition affecting up to one in five Australian women of reproductive age. Women with PCOS have higher rates of obesity and longitudinal weight gain. PCOS is a thus a valuable model for studying obesity-related health in young women since it provides the opportunity to target a large group of women early in life to prevent weight gain and associated obesity complications in themselves and their offspring. For overweight and obese women with PCOS, weight loss is the first-line therapy. Our preliminary data strongly suggest disturbances in appetite control, energy expenditure, and psychological health as mechanisms to explain the difficulties in weight management that women with PCOS commonly experience.

This project will consist of a randomised controlled trial comparing a multidisciplinary lifestyle (diet, exercise and behaviour) weight management intervention with standard care in overweight and

obese women with PCOS. The intervention consists of 3 months weight loss and 9 months weight maintenance and the honours project will focus on the 3 month weight loss component. Key outcomes analysed will include weight and body composition, reproductive hormones, metabolic outcomes (insulin, glucose, lipids), psychological variables (anxiety, depression, quality of life), appetite regulation and energy expenditure and the relationship of key psychological and physiological mechanisms to weight management and attrition in PCOS. The honours student will assist in recruitment, clinical measurements and administration of the lifestyle intervention and laboratory analysis of samples.

References

- Moran LJ, Hutchison SK, Norman RJ, Teede HJ 2011 Lifestyle changes in women with polycystic ovary syndrome. Cochrane database of systematic reviews 2
- Moran LJ, Noakes M, Clifton PM, Wittert GA, Tomlinson L, Galletly C, Luscombe ND, Norman RJ 2004 Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. The Journal of clinical endocrinology and metabolism 89:3337-3344

PROJECT: Dietary knowledge in Polycystic Ovary Syndrome

Contact Person
Dr Lisa Moran
Phone: 8313 1352
lisa.moran@adelaide.edu.au
http://www.adelaide.edu.au/directory/lisa.moran

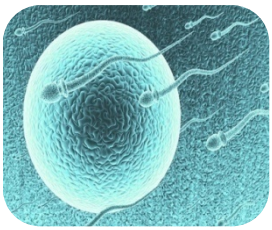
Project Background/Aims

Up to half of Australian reproductive-aged women are overweight or obese, with weight-associated risks of infertility and adverse effects on the health of the offspring. Overweight and obesity significantly worsen the reproductive, metabolic and psychological implications of polycystic ovary syndrome (PCOS) – a serious endocrine condition affecting up to one in five Australian women of reproductive age. Women with PCOS have higher rates of obesity and longitudinal weight gain and weight management is the recommended initial treatment strategy for PCOS. Dietary advice is a key component of a weight management program and current evidence-based Australian guidelines outline the principles of dietary management for PCOS. However, the effect of these guidelines on actual dietary prescription by health professionals and subsequent dietary intake by women with PCOS is not known. In the absence of specific recommendations by health professionals, women with PCOS also often seek non-evidence based sources of information on dietary management. The effect of this on actual dietary intake is not known. Furthermore, despite the Australian PCOS guidelines being the only international evidence-based guidelines for lifestyle management in PCOS, their relative uptake in Australia compared to other countries is not known. The aims of this project are to assess the knowledge of women with PCOS of dietary recommendations, specifically their overall knowledge, the sources this knowledge was obtained from and their opinion of this knowledge, and to assess the association between this knowledge and quantitative measures of dietary intake. This project will involve the development and piloting of a survey on dietary knowledge and intake in women with PCOS and without PCOS. This study will also seek to assess women with and without PCOS across a number of geographical locations (Australia, USA and UK).

References

- Jeanes YM, Barr S, Smith K, Hart KH 2009 Dec;22(6):551-8. Dietary management of women with polycystic ovary syndrome in the United Kingdom: the role of dietitians. J Hum Nutr Diet.
- Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BG, Wong JL, Norman RJ, Costello MF 2011 Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. The Medical journal of Australia 195:S65-112

Gamete and Embryo Biology Laboratory



Supervisors

Dr Michelle Lane
Dr Deirdre Zander-Fox
Dr Tod Fullston
Dr Nicole McPherson

Location: Medical School

Contact Person
Dr Michelle Lane
Phone: 8313 8176
michelle.lane@adelaide.edu.au

PROJECT: Making old eggs young.

Project Background

An increasing number of women seek IVF treatment as a result of declining fertility, associated with advanced maternal age. However, despite popular misconceptions that IVF can cure all infertility, IVF cannot cure aged eggs. It is currently this group of patients who often do not reach their goal of a baby without repeated treatment with its emotional and financial toll. Mitochondrial function is the powerhouse of the cell and mitochondrial activity has been shown to reduce with age resulting in a significant reduction in egg and embryo viability. The aim of this study is to examine the ability of novel mitochondrial nutrients for their ability to rescue mitochondrial function in aged eggs and embryos to improve pregnancy rates.

This study will investigate embryo development and viability after culture in different media formulations of mitochondrial nutrients. Techniques will involve general embryology, assessment of metabolism, epi- and confocal microscopy, general molecular methods such as q-PCR.

Information from this study will assist in developing new media to improve IVF procedures.

PROJECT: Interaction of male obesity and molecular function of human sperm on IVF outcomes.

Project Background

There is increasing awareness that male obesity has a negative impact on sperm quality. Male obesity is now known to be associated with reduced success rates after IVF treatment as well as increases in miscarriage and pregnancy loss. However, the mechanism for this impact on pregnancy health is largely unknown. The aim of this study is to examine the impact of paternal obesity at the time of conception on the molecular structure of the sperm and how this impacts on fertilization, embryo development and pregnancy after IVF treatment.

This study will investigate sperm motility, count, reactive oxygen species, methylation and acetylation of sperm in relation to fertilization, sperm binding and embryo development. Techniques will involve general andrology methods as well as immunohistochemistry, epi- and confocal microscopy, mitochondrial measurement and cell culture.

PROJECT: New methods for selecting human embryos for transfer.

Currently, in a human IVF cycle the selection of which embryo to transfer is usually based on the morphology (or how the embryo looks down the microscope). However, morphology is poorly correlated with pregnancy rates. Therefore, there is a pressing need to be able to non-invasively select the best embryo for transfer.

This study will assess the metabolic output of human embryos and relate the metabolic fingerprint of the embryo to its chromosomal content and its subsequent viability after transfer.

This study will give the student exposure to clinical IVF laboratory and an understanding of human IVF. Techniques will involve assessment of metabolism using epifluorescence and several biochemical assays, and molecular techniques including next generation sequencing.

Neuromotor Plasticity and Development (NeuroPAD)


Supervisors:

Dr Julia Pitcher
Assoc/Prof Michael Ridding

Location: Robinson Research Institute,
Norwich Centre, 77 King William Road, North Adelaide, SA 5006

The Neuromotor Plasticity and Development (NeuroPAD) group investigates the way that the brain, nerves, and muscles create and control movement in the human body.

There are two major aims of the research conducted at the NeuroPAD. Firstly, the group is interested in how the early environment (both during pregnancy and after birth) influences development of the cortex areas of the brain, and how this affects motor, cognitive and behavioural function during childhood and older age. We are particularly interested in how preterm birth influences the brain mechanisms underlying learning and memory.

The second major aim is to develop new treatments that will rehabilitate impaired motor function in those suffering from brain injuries or altered brain development, such as stroke victims and preterm children.

Project: The Development of Motor Inhibition After Preterm Birth in Humans.

Supervisor
Dr Julia Pitcher
Phone: 83131301
julia.pitcher@adelaide.edu.au

Project Background

Fine motor control of human hand and finger muscles is partly reliant in the activity in a special class of neurons called interneurons in the motor cortical areas. Healthy dexterous movements are thought to rely on a balance between the relative influence of excitatory and inhibitory interneurons on motor output neurons. Inhibitory interneurons controlled by the neurotransmitter GABA are thought to enable selective activation of the muscles needed for a given movement, by gating out or "inhibiting" interference from other muscles not involved in the movement. In humans, the relative strength of these interneuronal pathways can be assessed using a non-invasive brain stimulation technique called transcranial magnetic stimulation (TMS), and recording the electrical activity in the hand muscle. We have shown in term-born healthy children, adolescents and young adults, that the inhibitory pathways reach adult levels of responsiveness before the age of 10 years. We have also shown that children and adolescents born preterm (i.e. before 37 completed weeks of gestation) have reduced excitability in the motor cortical area of the brain and a reduced ability to perform fine motor tasks with their hands. Others have shown, using other techniques and tasks, that preterm children have difficulties inhibiting unwanted actions, and gating out stimuli not relevant to the task at hand. These lines of evidence suggest that preterm birth may alter or delay the development of the inhibitory interneuronal pathways in particular.

In this study, you will learn to use TMS and electromyography techniques, as well as behavioural tests of fine motor control, to examine intracortical inhibition in the motor cortex region of adolescents and young adults who were born preterm. You will test the hypothesis that intracortical inhibition is reduced in individuals born preterm, and that this is functionally evident as reduced manual dexterity when performing fine motor tasks. In terms of the big picture, the ability to modulate the activity of these inhibitory pathways is a key feature of neuroplasticity – the key mechanism underlying learning and memory. Preterm children commonly have difficulties with learning and memory. One underlying mechanism might be abnormal development of intracortical inhibition that adversely affects neuroplasticity.
This project would best suit a student who has some knowledge of human neurophysiology.

References:

- Pitcher JB, Schneider LA, Burns NR, Drysdale JL, Higgins RD, Ridding MC, Nettelbeck TJ, Haslam RR, and Robinson JS. (2012). Reduced corticomotor excitability and motor skills development in children born preterm. *Journal of Physiology* 590(22): 5827 – 5844.
- Pitcher JB, Riley AM, Doeltgen SC, Kurylowicz L, Rothwell JC, McAllister SM, Smith AE, Clow, A, Kennaway DJ, Ridding MC. (2012). Physiological Evidence Consistent with Reduced Neuroplasticity in Human Adolescents Born Preterm. *Journal of Neuroscience* 32(46): 16410-16416.
- Gilbert DL, Isaacs KM, Augusta M, MacNeil LK, Mostofsky SH (2011). Motor cortex inhibition: A

marker of ADHD behavior and motor development in children. *Neurology* 76(7): 615-621.

Project: Do skin receptors modulate motor cortex inhibition normally in individuals born preterm?

Supervisor
Dr Julia Pitcher
Phone: 83131301
julia.pitcher@adelaide.edu.au

Project Background

Neuroplasticity is the brain's ability to change the strength of its neural connections in response to incoming stimuli and experience. The neurophysiological mechanisms underlying neuroplasticity are believed to be the key processes responsible for learning and memory. In awake humans, neuroplasticity can be evoked and measured using non-invasive techniques called transcranial magnetic brain stimulation (TMS). Experimentally, neuroplasticity is often studied in the motor cortex (the major movement area) as it is one of the few areas of the brain whose direct output can be evoked (using TMS) and measured non-invasively i.e. by measuring changes in muscle activation using surface electromyography.

Under normal resting circumstances, the neurons within the motor cortex are more inhibited than they are excited, preventing unwanted movements. Various experimental studies have shown that, in order for neuroplastic changes to occur in the motor cortex, this so-called "tonic inhibition" must be reduced. One of the most efficient ways to reduce motor cortex inhibition physiologically is by input to the sensory and motor cortices from sensory receptors in the periphery e.g. by stimulating skin touch receptors in the fingers. This appears particularly important for learning fine, dexterous skills with the hands, such as writing or knitting.

We can test how efficiently sensory input from the periphery reduces motor cortex inhibition by pairing very mild electrical activation of the finger pads with a paired pulse TMS technique that measures motor cortex inhibition. Using this technique, we have previously shown that integration of this sensory input in the cortex is reduced when you get old, and may influence the ability to learn and perform new dexterous skills.

We have also shown that children born preterm have a reduced capacity for neuroplasticity that may underlie some of their difficulties with learning and memory. A number of other lines of evidence from our work, and others, suggest that this is related to abnormal cortisol hormone levels and possibly altered sensory-motor integration of afferent signals (i.e. nerve signals from receptors in the periphery to the brain). In this project you will learn how to evoke and measure different peripherally evoked potentials, and use TMS and surface electromyography to answer two main questions:

1. Are sensory evoked potentials and/or cutaneo-muscular reflexes altered in individuals born preterm?
2. Is their ability to reduce motor cortex inhibition with cutaneo-afferent input altered?
3. If so, does this adversely affect their ability to learn a dexterous motor task?

This project would best suit a student who has some knowledge of human neurophysiology.

References:

- • Pitcher JB, Schneider LA, Burns NR, Drysdale JL, Higgins RD, Ridding MC, Nettelbeck TJ, Haslam RR, and Robinson JS. (2012). Reduced corticomotor excitability and motor skills development in children born preterm. Journal of Physiology 590(22): 5827 – 5844.
- Pitcher JB, Riley AM, Doeltgen SC, Kurylowicz L, Rothwell JC, McAllister SM, Smith AE, Clow, A, Kennaway DJ, Ridding MC. (2012). Physiological Evidence Consistent with Reduced Neuroplasticity in Human Adolescents Born Preterm. Journal of Neuroscience 32(46): 16410-16416.
- Gilbert DL, Isaacs KM, Augusta M, MacNeil LK, Mostofsky SH (2011). Motor cortex inhibition: A marker of ADHD behavior and motor development in children. Neurology 76(7): 615-621.
- Smith AE, Ridding MC, Higgins RD, Wittert GA & Pitcher JB (2011). Cutaneous afferent input does not modulate motor intracortical inhibition in ageing men. European Journal of Neuroscience 34(9): 1461-1469

Obesity Research Group



Supervisors (photographs left to right)
Professor Jodie Dodd
Dr Rosalie Grivell
Dr Lisa Moran

Location: Women's and Children's Hospital/ Medical School

Contact Person
Andrea Deussen
Phone: 8313 1429
andrea.deussen@adelaide.edu.au

The Obesity Research Group, led by Professor Jodie Dodd and Dr Rosalie Grivell, conduct high quality randomised trials, research evaluation, synthesis and translation directly related to the short and long term health of women and their infants with a particular focus on the effect of diet and lifestyle interventions. Other research interests include maternal fetal medicine and multiple pregnancy. The group evaluates and translates relevant research for the health of women and babies and collaborates nationally and internationally with groups with similar research interests.

Good nutrition and physical activity are important for women of reproductive age, particularly during pregnancy. The risk of pregnancy complications, including high blood pressure, pre-eclampsia, gestational diabetes and caesarean birth increases with maternal BMI, and may be improved through optimal nutrition and exercise.

The group investigates the effect of diet and lifestyle interventions during pregnancy on pregnancy complications and infant health outcomes. Optimal nutrition and exercise during pregnancy may reduce the risk of poor infant health including high birth weight, nursery admissions, as well as an increased lifetime risk of subsequent obesity and cardiovascular disease.

In 2014 the findings of the LIMIT randomised controlled trial were published, involving 2,212 pregnant women who were overweight or obese. Women who received dietary and lifestyle advice made significant improvements to both their diet and physical activity patterns. Additionally, their babies were less likely to be born with a birth weight above 4kg. Ongoing follow-up of the children continues. Ongoing randomised trials are currently evaluating the role of metformin as an adjuvant therapy to dietary interventions among women who are overweight or obese (the GRoW randomised trial), and the evaluation of dietary interventions among women of normal BMI as a tool to prevent weight retention following birth (the OPTIMISE randomised trial).

Each of the projects specified below are in conducted in the context of these established randomised trials evaluating antenatal dietary and lifestyle interventions.

PROJECT: Does an elevated blood glucose level in women during first trimester of pregnancy identify risk of subsequent 1) adverse pregnancy outcomes including gestational diabetes and 2) adverse infant outcomes including large for gestational age birth weight, respiratory distress syndrome and nursery admission?

Project Background/Aims

Gestational diabetes, if left untreated is associated with adverse maternal and infant outcomes. While screening for gestational diabetes occurs late in the second trimester of pregnancy, it is likely that disturbances to glucose metabolism occur at a subclinical level earlier in pregnancy. This project will evaluate whether the simple measurement of blood glucose early in pregnancy can identify women who are at risk of developing gestational diabetes and other associated adverse infant outcomes.

PROJECT: What is the relationship between maternal serum markers of glucose metabolism at 28 weeks of pregnancy, and in cord blood collected at birth, with clinical newborn outcomes (including high birth weight and respiratory distress syndrome) and newborn measures of adiposity?

Project Background/Aims

There is evidence that the intrauterine environment plays a key role in the programming of subsequent overweight and obesity in chidren. An infant who is born large for gestional age (or with birth weight above 4kg) is at increased risk of developing obesity in both childhood and adulthood. This project will evaluate the associations between measures of

maternal glucose metabolism and newborn infant measures of adiposity, as a potential tool to identify earlier children who are at the greatest risk and therefore initiate earlier opportunities for prevention.

PROJECT: Is it possible to identify women at risk of gestational diabetes, pre-eclampsia, and preterm birth from their dietary intake in early pregnancy?

Project Background/Aims

Findings from the LIMIT randomised trial have shown that improving women's dietary intake of fruits, vegetables and fibre, and reducing the intake of saturated fats is associated with a reduction in infant birth weight above 4 kg and respiratory distress syndrome. This project will evaluate the associations between dietary intake (including key macro and micro nutrients) and risk of adverse pregnancy outcomes. Will we one day see dietary prescriptions for women in early pregnancy?

PROJECT: What is the relationship between infant inflammatory markers (measured in cord blood at birth) and subsequent child neurodevelopment?

Project Background/Aims

Maternal overweight and obesity is associated with a range of pregnancy and birth outcomes. Increasingly there is recognition of an association between maternal obesity and subsequent child neurodevelopmental outcomes, including an increased risk of impaired cognition and attention defecit hyperactivity disorder. It is postulated that the low grade inflammatory processes and cytokines observed in the setting of obesity may play a role in neurodevelopment.

PROJECT: The influence of maternal overweight and obesity, and gestational weight gain on infant and early childhood neurodevelopment.

Project Background/Aims

Maternal overweight and obesity, and high gestational weight gain in pregnancy are both independent risk factors for adverse pregnancy outcomes. This project will evaluate the effect of increasing maternal BMI and gestational weight gain on infant and early childhood neurodevelopment. There is evidence that the intrauterine environment plays a key role in neurodevelopmental programming in early childhood. This project will evaluate the associations between maternal BMI and infant and early childhood neurodevelopment.

PROJECT: The influence of cardiometabolic markers measured in infant cord blood at birth on weight and measures of infant and early childhood adiposity.

Project Background/Aims

There is evidence that the intrauterine environment plays a key role in the programming of subsequent overweight and obesity in chidren. An infant who is born large for gestional age (or with birth weight above 4kg) is at increased risk of developing obesity in both childhood and adulthood. This project will evaluate the associations between cardiometabolic measures and measures of adiposity in infancy and early childhood, as a potential tool to identify earlier children who are at the greatest risk and therefore initiate earlier opportunities for prevention.

Ovarian Cell Biology Group

Supervisors

Dr Rebecca Robker
Michael Barry (M.Sc.)
Ryan Rose (B.HSc.(Hons))(not pictured)
Dr Linda Linyan Wu (Not pictured)
Dr Michelle Lane (not pictured)

Location: Medical School, Robinson Research Institute, Fertility SA, (St Andrews Hospital, South Tce, Adelaide)

Contact Person
Dr Rebecca Robker
8313 8159
rebecca.robker@adelaide.edu.au

A major research interest of our team is to understand how the metabolic and inflammatory disturbances that result from obesity and Polycystic Ovary Syndrome (or PCOS), affect female fertility. Using a mouse model of diet-induced obesity, we have shown that insulin resistance is associated with impaired oocyte developmental competence and altered blastocyst formation. These studies showed, for the first time, that the detrimental effects of obesity on female reproduction and embryo development commence with dramatic alterations in oocyte quality. We have since found that cumulus-oocyte-complexes of obese mice contain high levels of lipid which is associated with endoplasmic reticulum stress. Follicles of obese women also contain increased lipid, increased inflammatory mediators and markers of endoplasmic reticulum stress. We are now elucidating the cellular pathways that regulate lipid storage and metabolism in the cumulus-oocyte-complex and determing how excessive lipid and inflammation impacts ovulation and oocyte developmental competence.

PROJECT: Oocyte lipid deposition and utilisation during embryogenesis

Supervisors
Dr Rebecca Robker
Michael Barry (M.Sc.)
Ryan Rose (B.HSc.(Hons))

Project Background

Oocytes are lipid-rich cells and the intracellular lipid stores within the oocyte at the completion of growth are thought to act as an energy reserve during fertilisation and preimplantation embryo development. Yet little is known about how oocytes accumulate and utilise this lipid during embryogenesis. Specific types of lipids also have differential effects on oocytes and embryos (i.e. physiological versus toxic lipids differentially affect stress responses, droplet accumulation and metabolism). This project will measure mitochondrial activity in mouse and humanoocytes and examine the energy generating processes of the embryo in its first days of life. The results will shape our fundamental understanding of embryogenesis and the developmental origins of health and disease.

Techniques will include isolation of oocytes and embryos from mice; immunohistochemical staining and confocal microscopy; and analysis of human oocytes. Project will provide training in basic science (oocyte biology, embryology, mitochondrial metabolism) as well as exposure to clinical embryology and reproductive medicine at an outstanding local IVF clinic.

References:

- Dunning KR, Russell DL, Robker RL. Lipids and oocyte developmental competence: the role of fatty acids and B-oxidation. Reproduction. 2014 Apr 23. [Epub ahead of print]
- Dunning KR, Anastasi MR, Zhang VJ, Russell DL, Robker RL. Regulation of Fatty Acid Oxidation in Mouse Cumulus-Oocyte Complexes during Maturation and Modulation by PPAR Agonists. PLoS One. 2014 Feb 5;9(2):e87327.
- Yang X, Wu LL, Chura LR, Liang X, Lane M, Norman RJ, Robker RL Exposure to lipid-rich follicular fluid is associated with endoplasmic reticulum stress and impaired oocyte maturation in cumulus-oocyte complexes Fertility and Sterility 2012 Jun;97(6):1438-43.
- Wu LL, Russell DL, Norman RJ, Robker RL Endoplasmic Reticulum (ER) Stress in Cumulus-Oocyte Complexes Impairs Pentraxin-3 Secretion, Mitochondrial Membrane Potential ($\Delta\Psi m$), and Embryo Development. Molecular Endocrinology 2012 Apr;26(4):562-73 Wu
- LL-Y, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ, Robker RL High fat diet causes lipotoxicity responses in cumulus-oocyte-complexes and decreased fertilization rates Endocrinology. 2010 Nov;151(11):5438-45.

Contact Person
Dr Linda Linyan Wu
8313 1512
Linda.linyanwu@adelaide.edu.au

PROJECT: Treatments for obese females to reverse the effects of obesity on offspring metabolic health.

Supervisors
Dr Linda Linyan Wu
Dr Rebecca Robker
Dr Michelle Lane

Project Background

Maternal obesity causes poor oocyte quality, low pregnancy rates and compromised offspring health. Offspring born from obese mothers are at high risk of developing metabolic diseases. A main research interest of our team is to identify the molecular mechanisms through which obesity impacts on ovarian function and oocyte quality which causes altered fetal growth during pregnancy and permanently 'programs' metabolism of offspring.

Obesity and lipid-rich environments cause excess lipid accumulation in non-adipose tissue, which triggers intracellular lipotoxicity responses including endoplasmic reticulum stress and mitochondrial dysfunction. We have found previously that obesity-induced lipotoxicicty responses cause poor oocyte quality and impaired embryo development, by using a genetically modified profoundly obese mouse model. Further, we have identified drug treatments that, given to obese mother mice during the oocyte maturation period, improves oocyte mitochondrial activity and viability and embryo quality. By using this novel current mouse model, the current project will investigate whether treating obese mother mice at the critical time window before fertilization has lasting beneficial effects and produces metabolically healthy offspring.

The project will provide training in physiology (mouse metabolic testing, glucose tolerance test (GTT), insulin tolerance test (ITT), hormone assays) as well as cellular and molecular techniques (mouse IVF and embryology, embryo transfer, western blot, immunohistochemical staining and confocal microscopy).

References

- Chen M, Wu L, Zhao J, Wu F, Davies MJ, Wittert GA, Norman RJ, Robker RL, Heilbronn LK.
- Altered glucose metabolism in mouse and humans conceived by in-vitro fertilization (IVF).
- Diabetes. 2014 Apr 23.
- Yang X, Wu LL, Chura LR, Liang X, Lane M, Norman RJ, Robker RL.
- Exposure to lipid-rich follicular fluid is associated with endoplasmic reticulum stress and impaired oocyte maturation in cumulus-oocyte complexes.
- Fertil Steril. 2012 Jun;97(6):1438-43.
- Wu LL, Russell DL, Norman RJ, Robker RL.
- Endoplasmic reticulum (ER) stress in cumulus-oocyte complexes impairs pentraxin-3 secretion, mitochondrial membrane potential (DeltaPsi m), and embryo development.
- Mol Endocrinol. 2012 Apr;26(4):562-73.
- Wu LL, Dunning KR, Yang X, Russell DL, Lane M, Norman RJ, Robker RL.
- High-fat diet causes lipotoxicity responses in cumulus-oocyte complexes and decreased fertilization rates.
- Endocrinology. 2010 Nov;151(11):5438-45.

Perinatal Health and Child Development


Supervisors
Dr Nicolette Hodyl
Associate Professor Michael Stark

Location: Robinson Research Institute,
Norwich Centre, 77 King William Road, North Adelaide, SA 5006

Contact Person
Dr Nicki Hodyl
Phone: 8313 1303
Email: nicolette.hodyl@adelaide.edu.au

The Perinatal Health and Child Development Group seeks to identify the impact of common adverse exposures in pregnancy that contribute to altered fetal growth, aberrant HPA function and altered immune development - which ultimately lead to poor child neurodevelopment and health outcomes.

This research links clinical and environmental exposures in the perinatal period to neonatal and child health outcomes, and spans basic science (assessing placental and cord blood biomarkers that lead to and/or predict poor outcomes) and epidemiology (examining outcomes in large cohorts).

Ultimately our group aims to identify aberrant processes and promulgate effective intervention strategies to optimise child health following exposure to an adverse in-utero environment.

Project: Cortisol diurnal rhythms in preterm neonates and the response to ante- and post-natal steroids: the impact of glucocorticoid receptor polymorphisms.

Supervisors
Dr Nicolette Hodyl
Assoc/Prof Michael Stark
Contact Person:
Dr. Nicolette Hodyl
Phone: 8313 1303
Nicolette.hodyl@adelaide.edu.au

Project Background

The incidence of preterm birth is increasing in Australia and currently accounts for over 24,000 preterm deliveries per year. Over 650 of these infants will die in the neonatal period while 18,000 will suffer neonatal and/or lifelong morbidity. Corticosteroids are essential for the development and maturation of fetal organs before birth. It has long been established that administration of antenatal corticosteroids is associated with reductions in adverse health outcomes in premature infants due to their role in accelerating fetal lung maturation. Often administration of postnatal corticosteroids to the preterm neonates is also required, to further assist with lung development. While this is crucial treatment to avoid neonatal respiratory morbidity, it is also associated with suppression of the fetal hypothalamic-pituitary-adrenal axis and fetal adrenal steroidogenesis, exerting long term effects on diurnal and stress induced cortisol levels.

Both cortisol and synthetic glucocorticoids act via the glucocorticoid receptor (GR). A number of single nucleotide polymorphisms in the GR gene exist, that are associated with altered sensitivity to glucocorticoids in adult populations. This study will assess the impact these polymorphisms have on diurnal cortisol rhythms in preterm neonates, comparing diurnal cycles between those exposed and unexposed to antenatal and postnatal steroids. This study may help explain why some preterm neonates appear more sensitive to the effects of steroids than their counterparts.

Placental Development Laboratory

Supervisors

Professor Claire Roberts
Professor Gus Dekker
Dr Tina Bianco-Miotto
Dr Amada Highet
Dr Prabha Andraweera
Dr Jessica Grieger

Location: Medical School North and Lyell McEwin Hospital

Contact Person
Professor Claire Roberts
Phone: 8313 3118
claire.roberts@adelaide.edu.au

A number of pathologies of pregnancy, including up to 50% of miscarriages, preeclampsia (hypertension and proteinuria in pregnancy), intrauterine growth restriction (IUGR), preterm labour, unexplained stillbirth and placental abruption are characterised by impaired cytotrophoblast invasion and an inadequate response of the uterine spiral arteries to undergo physiological transformation. Together these conditions affect more than one quarter of pregnant women in developed societies. Our laboratory takes a "bench to bedside" approach to discovery and solving clinical problems in pregnancy that have their origins in placental development and maternal adaptation to pregnancy. We undertake basic cellular and molecular experiments to elucidate mechanisms that govern normal and abnormal placental development. We also have a strong focus on identifying genetic, nutritional, lifestyle and clinical factors that associate with pregnancy outcome in the SCOPE and PAPO pregnancy cohorts. Current projects include single nucleotide polymorphisms in mother, father, baby trios in prediction of pregnancy complications, the role of vitamin D, folate, selenium and zinc in placentation and pregnancy outcome (in humans and mice), the role of hypoxia in placental development, and sex differences in the human placental transcriptome in normal and complicated pregnancies.

PROJECT: The role of micronutrients in placental function and pregnancy outcome

Supervisors
Prof Claire Roberts
Prof Gus Dekker
Dr Prabha Andraweera
Dr Amanda Highet
Dr Tina Bianco-Miotto

Project Background

Pregnancy complications such as preeclampsia, intrauterine growth restriction, gestational diabetes and preterm birth affect about 20% of human pregnancies. These pregnancy complications predict lifelong health and sometimes mortality for the baby and/or the mother. Deficiencies in micronutrients in the mother's diet including folate, vitamin D, selenium and zinc prior to and during pregnancy have been implicated in these adverse pregnancy outcomes. Exciting research in our laboratory has found clear associations between maternal micronutrient status and pregnancy outcomes. This series of projects investigates the associations of micronutrient status and pregnancy outcome as well as the role of the placenta in this association.

The first project will determine the association of maternal micronutrient status in early pregnancy with pregnancy complications and fetal growth. Maternal blood samples from pregnant women in our large pregnancy cohort will be assayed for a variety of macronutrients. Data on maternal diet, use of micronutrient supplements, clinical and socio-economic factors will be analysed together to determine how micronutrients combine to influence pregnancy outcome. The student will develop skills in ELISA, colorimetric assays and Western blotting, as well as biostatistical analyses. The student will interact with obstetricians and midwives as well as scientists.

The second project will focus on the role of the placenta in mediating the effects of maternal

micronutrient status on pregnancy outcome. The placenta has a very important role in providing nutrition for optimal growth and development of the baby. First trimester and term placental explants will be used in cell culture experiments to determine the effects of folate, vitamin D, selenium and zinc on changes in placental explant growth, apoptosis, development and gene expression. Investigating the effect of micronutrients on placental function has the potential to determine factors that go awry in the placenta during early pregnancy leading to placental insufficiency and adverse outcomes.

The project will involve placental explant cultures, qPCR, TUNEL, and immunohistochemistry.

PROJECT: Sex differences in placental gene expression and the X chromosome.

Supervisors
Prof Claire Roberts
Dr Tina Bianco-Miotto

Project Background

We aim to demonstrate for the first time that X chromosome genes include many that are important in placental development and function and maternal adaptation to pregnancy, and that some of these escape X inactivation and are therefore differentially expressed by the male and female placenta. Most research on this to date has been conducted in mice which emerging evidence shows is unlike the human. Hence we expect our data will challenge established dogma. We expect our research will explain the different patterns of fetal growth observed in males and females before birth. This project will utilise our access to human placental tissues and skill and knowledge base in placental development, fetal growth and epigenetics. This project will involve gene expression analyses of X chromosome genes as well as epigenetic analysis of differentially expressed genes.

PROJECT: Unraveling the molecular underpinnings of human sex-dependent developmental strategies *in utero.*

Supervisors
Prof Claire Roberts
Dr Tina Bianco-Miotto

Project Background

In humans, as in other mammals, females not only live longer but have better survival prospects than males for many diseases. The period of fetal development is no exception. During intrauterine development, there are distinct sex differences in fetal growth trajectories and birth weight, with a sex bias in the prevalence of preterm birth, pregnancy complications such as preeclampsia and perinatal death. However, very little is known about the differences between the sexes in the placenta at the molecular level, or about how this may predispose one sex to be at an increased risk of a pregnancy complication compared to the other.

Using our large bio-bank of human samples, we are investigating the sex-dependent developmental strategies adopted by males and females *in utero* by using the latest RNA sequencing, microarray and SNP genotyping methodologies to study microRNAs as well as long non-coding and protein-coding RNA molecules. We have several project possibilities in this area for students interested in human molecular genetics and who possess a strong molecular biology and/or bioinformatics background. The candidate will acquire skills in nucleic acid isolation, preparation and quality control, as well as gene expression and bioinformatics analyses. Additional opportunities are available in placental cellular manipulation and validation of sex-based developmental differences.

The outcomes of this research will help to understand what factors drive sex-dependent human developmental patterns, largely through studying the fetal-maternal interactions in the human placenta.

PROJECT: Obesity is associated with increased inflammation and oxidative stress in the placenta.

Supervisors
Prof Claire Roberts
Dr Tina Bianco-Miotto

Project Background

Pregnancy complications such as preeclampsia, preterm birth, intrauterine growth restriction and gestational diabetes afflict 25% of first pregnancies and can be life threatening to the mother and/or baby. Maternal obesity is becoming alarmingly common with over 50% of pregnant women being overweight or obese. Normal pregnancy is an inflammatory state that facilitates pregnancy success but this can be worsened by poor diet and maternal obesity since obesity also increases inflammation. Although micronutrients are only needed in small amounts for health, many are important in preventing inflammation and oxidative stress that are common features of pregnancy complications. Maternal obesity and micronutrient deficiencies may interact to further put women at an increased risk of pregnancy complication. Defining how obesity and micronutrients interact will help identify nutritional intervention strategies for reducing the risk of pregnancy complications in these women.

In this project the student will manipulate micronutrient levels in human primary trophoblast cells derived from term placenta and assess changes in placental proliferation, apoptosis and inflammation/oxidative stress pathways. These experiments will be performed in term explants collected from lean and obese women and

responses to oxidative stress and manipulation of micronutrients will be assessed in these cultured cells. The techniques utilised in this project include placental cell culture, immunohistochemistry and quantitative PCR.

PROJECT: Epigenetic regulation in placenta development.

Supervisors
Prof Claire Roberts
Dr Tina Bianco-Miotto

Project Background

The best known function of the placenta is to mediate fetal-maternal exchange throughout pregnancy but it also plays a major role in directing maternal adaptation to pregnancy by secreting a variety of steroid and peptide hormones that modulate maternal physiology without which pregnancy could not be sustained. The placenta is a unique organ in several respects. Firstly, although the placenta is a shared organ between mother and fetus, it is an extra-embryonic tissue and is therefore primarily regulated by the fetal genome. Secondly, the placenta separates from mother and fetus after birth, making it a truly transient organ. For this reason, the epigenetic mechanisms involved in placenta development may not be under the same constraints as other somatic tissues. In humans, placental development begins shortly after an embryo implants into the lining of the uterus, where it begins by invading and remodelling the uterine spiral arterioles to acquire a maternal blood supply for efficient feto-maternal exchange. This invasive process is similar to cancer metastasis and is strictly controlled both spatially and temporally in humans through mechanisms that are not fully understood.

This project will utilise human placenta tissues and use the following techniques: immunohistochemistry, qPCR for gene expression, DNA methylation analyses by high resolution melting after bisulphite modification. By determining how epigenetic profiles change in the placenta throughout pregnancy and in response to adverse outcomes or environmental exposures we can identify epigenetic biomarkers indicative of future risk of pregnancy complications. Epigenetic modifications are also reversible so these changes may also be targets for therapeutic intervention. This project will suit a student interested in learning molecular techniques and working with nucleic acids.

Project: Genetic and environmental risk for pregnancy complications and subsequent metabolic syndrome

Supervisors

Prof Claire Roberts
Prof Gus Dekker
Dr Prabha Andraweera
Dr Jessica Grieger

Project Background

Coronary artery disease (CAD) affects 1.4 million Australians and is the cause of 14% of all deaths in Australia. Pregnancy can be considered as a physiological stress test that identifies women at risk of future vascular disease. Current evidence demonstrates that women who develop certain pregnancy complications are at increased risk of morbidity and mortality from CAD. Recurrent miscarriage and pregnancies complicated by preeclampsia (PE), small for gestational age (SGA) infants, gestational diabetes mellitus (GDM) and spontaneous preterm birth (sPTB) are associated with a 50-300% increased risk of CAD. Metabolic syndrome (MeS) is a strong risk factor for CAD and refers to the presence of obesity, insulin resistance, dyslipidaemia and hypertension. At present, there is a paucity of literature on the relationship between pregnancy complications and postpartum MeS. We have recently published many papers on the SCOPE study. The SCOPE study is an international, multi-center, prospective cohort study with the aim of developing screening tests to predict preeclampsia, SGA infants, and preterm birth across different populations. We recruited 1164 mother-father-baby trios to the Adelaide cohort of the SCOPE study between September 2005 and September 2008. We have a large collection of data from these women and their partners obtained at both 15 and 20 weeks of gestation, at the time of diagnosis of any adverse pregnancy outcomes and at term and data from the babies at birth. We also have family history data and health information about the women's parents. In addition, we have genotype data from parents and infants for 100 single nucleotide polymorphisms. We aim to follow the women of the SCOPE study 10 years after delivery of the first child to identify the prevalence of metabolic syndrome and to identify genetic and antenatal risk factors that predict metabolic syndrome following pregnancy complications.

Project: Genetic and early life determinants of childhood obesity

Supervisors

Prof. Claire Roberts
Prof. Gus Dekker
Dr. Prabha Andraweera
Dr Jessica Grieger

Project Background

Obesity, which is one of the most important global epidemics of present times, is increasing in all age groups. To date, strategies devised for treatment and prevention of obesity have been disappointing and novel approaches are required. Over 50% of the adult population in Australia is either overweight or

obese and the epidemic has now reached children with approximately 21-25% of 2-18 year olds being classified as overweight and 5-6% as obese. Childhood obesity is a risk for adult obesity and its attendant health problems including metabolic syndrome, type 2 diabetes, hypertension and coronary artery disease. Emerging evidence demonstrates a link between intrauterine life and childhood obesity. However, the findings are hindered due to inadequate data on maternal, paternal and infant characteristics, lack of information on environmental and life style factors, lack of prospective data and lack of DNA from the parents and child. Consequently, the relative roles of pregnancy and childhood environmental and lifestyle influences, as well as interactions between genetic and environmental factors that contribute to childhood obesity remain poorly defined. We propose a follow up study of 10 year olds from the SCOPE (Screening for Pregnancy Endpoints) study. The SCOPE study was conducted in Adelaide during 2005-2008 and 1164 nulliparous pregnant women, their partners and babies were recruited. Detailed information was collected at 15 and 20 weeks gestation and at the time of delivery of the baby.

We aim to identify genetic and antenatal modifiable determinants of childhood obesity.

PROJECT: Antioxidant responses in first trimester trophoblasts.

Supervisors
Prof Claire Roberts
Dr Tina Bianco-Miotto
Dr Amanda Highet

Project Background

Oxygen tension within the human placenta increases rapidly at the end of the first trimester of pregnancy, when the flow of maternal blood to the intervillous space is established. With this increase in oxygen tension comes a temporary burst of oxidative stress in the placental cells. If oxidative stress is not carefully controlled, placental development can be affected, increasing the risk of miscarriage or preeclampsia. We are studying antioxidant responses in first trimester placental cells called trophoblasts. In particular, the role of the transcription factor NF-E2-related factor 2 (Nrf2), which is a master regulator of the cellular antioxidant response that can be induced by micronutrients believed to be important for placental development.

References:

E. Jauniaux, L. Poston, G.J. Burton, Placental-related diseases of pregnancy: Involvement of oxidative stress and implications in human evolution, Hum Reprod Update, 12 (2006) 747-755.

Other associated projects may be negotiated.

Reproductive Biotechnology Group

Supervisors
Associate Professor Mark Nottle
Dr Ivan Vassiliev
Location: Medical School

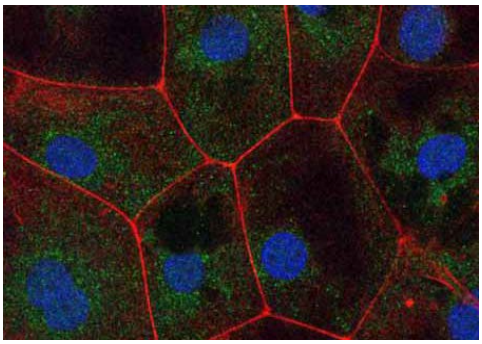
Contact Person
A/Prof Mark Nottle
8313 4087
mark.nottle@adelaide.edu.au

The Reproductive Biotechnology group has an international reputation in the general areas of reproductive biology and the development of associated technologies for biomedical and agricultural applications. In collaboration with a number of university, institute and hospital research groups in Australia as well as overseas, current research is focused on developing organ, tissue and cell replacement therapies.

PROJECT: Making embryos for Research.

Project Background

Our Laboratory uses in vitro produced (IVP) pig embryos for much of its research. This uses abattoir derived ovaries from which oocytes are removed, matured in culture, fertilised and then cultured up to six days. While IVP can produce embryos for research purposes these are of a lesser quality than those that would be found in the reproductive tract. The current project aims to improve one or more steps in this process so that we can ultimately produce embryos of the same quality. Project s are available in this general area and will provide students with research experience across a range of areas including molecular and cell biology and embryology.



PROJECT: Reducing early embryonic loss.

Project Background

Around 30% of embryos are lost early in pregnancy, with the reasons for this unknown. Our Lab is examining the hypothesis that the majority of these losses are due to differences in oocyte quality as a result of changes in nutrition , season, disease etc. In particular we are examining how these influence oocyte quality and embryo development. Projects are available in this general area and will provide students with research experience across a range of areas including molecular and cell biology and embryology.

PROJECT: Isolation and characterisation of embryonic stem cells.

Project Background

As human stem cell research advances there is an increasing need for a large animal model for bridging the gap between mouse studies and clinical trials. We have developed a new method for isolating ESCs and are using this to develop the pig as a large animal model for stem cell research. This includes the isolation and characterisation of embryonic stem cells from a range of species and sources including parthenogenetic embryos. Project s are available in this general area and will provide students with research experience in cell biology, embryology and stem cells.

Reproductive Cancer Research Group



Supervisors

Dr Carmela Ricciardelli
Professor Martin Oehler
Associate Professor Darryl Russell

Location: Medical School

Contact Person
Dr Carmela Ricciardelli
Phone: 8313 8255
carmela.ricciardelli@adelaide.edu.au

Dr Ricciardelli, a Cancer Cell Biologist, joined the Department in April 2005. Dr Ricciardelli was awarded her Ph D in 1996 (Flinders University) and has undertaken postdoctoral studies in the Department of Surgery, Flinders Medical Centre, South Australia (1996-2001) and Dame Roma Mitchell Cancer Research Laboratories, Hanson Institute, South Australia (2002-2005). In 2007 she was the recipient of the Hilda Farmer Fellowship in Faculty of Health Sciences, University of Adelaide which has enabled her to build a Reproductive cancer research group in Discipline of Obstetrics and Gynaecology at University of Adelaide. In 2012 Dr Ricciardelli was awarded a Senior fellowship by Cancer Council SA/SAHMRI. Dr Ricciardelli's current research focuses on further understanding the cross talk between cancer cells and the tumour microenvironment and mechanisms whereby the tumour microenvironment promotes the spread of breast, prostate and ovarian cancers.

PROJECT: The annexin A2 signalling pathway: Novel therapeutic targets for ovarian cancer.

Supervisors
Dr Carmela Ricciardelli
Dr Noor Lokman
Prof Martin Oehler

Project Background

The tumour microenvironment - composed of blood vessels, leukocytes, stem cells, fibroblasts, and the extracellular matrix (ECM) - is increasingly implicated as a key controlling factor in tumour progression. This is particularly the case for the growth and progression of solid tumours such as ovarian cancer. Using a novel approach we modelled the metastatic microenvironment *in vitro* and explored the two-way interactions between ovarian cancer cells and peritoneal cells using proteomics analysis. This strategy identified several proteins that are specifically modulated by ovarian cancer cells when they interact with the peritoneum to maximise tumour cell attachment and survival. One of these proteins is the phospholipid calcium binding protein, annexin A2. Annexin A2 forms a complex with S100A10 and together they play a critical role in the plasminogen activator system to mediate the conversion of plasminogen to plasmin, a key enzyme which facilitates essential cellular processes involved in cancer invasion. We have recently shown that annexin A2 is highly expressed in 90% of serous ovarian cancers (most common subtype) and is actively involved in the process of ovarian cancer metastasis. Several annexin A2 targeting strategies are available to either block annexin A2 function (annexin A2 peptide, annexin A2 blocking antibodies, src inhibitor to block annexin A2 phosphorylation), inhibit annexin A2 synthesis (annexin A2 siRNA, all trans retinoic acid) or block the interaction with annexin A2 interacting proteins (S100A10 blocking antibody, S100A10 siRNA & plasmin inhibitors). This project will assess the effectiveness of these inhibitors to inhibit serous ovarian cancer invasion using in vitro and in vivo models of ovarian cancer. This project will utilise a broad range of techniques including cell motility, cell invasion, western blotting,immunohistochemistry, qPCR and in vivo ovarian cancer models.

Aim 1. Identify effective annexin A2 pathway inhibitors that block ovarian cancer growth and invasion using *in vitro* and *in vivo* models.

Aim 2: Evaluate whether annexin A2 inhibitors synergize with 1st line chemotherapy using in vitro and in vivo models.

PROJECT: Targeting the hyaluronan signalling pathway to overcome chemoresistance.

Supervisors
Dr Carmela Ricciardelli
Prof Martin Oehler

Project Background

Ovarian cancer is the most lethal gynaecological cancer and the development of chemoresistance results in significant mortality. Over 80% of patients treated via chemotherapy eventually relapse and become resistant to chemotherapy. A well established cause of chemoresistance involves the increased expression of ABC membrane transporter proteins, which act to decrease levels of chemotherapy drugs within cells. Although effective in in vitro studies, clinical trials investigating ABC transporter inhibitors have failed to significantly improve patient survival, mainly due to focus on only a limited number of ABC transporters. Innovative treatment strategies to overcome chemoresistance are therefore urgently required. Our recent studies have linked chemoresistance with the production of the extracellular matrix component hyaluronan (HA). HA

plays an important role in promoting attachment of cancer cells to peritoneal cells via interactions with the HA receptor, CD44. We have shown that HA can increase the expression of ABC transporters in ovarian cancer cell lines expressing the HA receptor, CD44, and thereby induce resistance to the chemotherapeutic drug, carboplatin. HA-CD44 interactions have been shown to activate several signalling pathways including the P13K, MAPK and Rho K pathways. Genes of the P13K/Akt cascade have also recently been shown to induce drug resistance to cisplatin. We plan to determine whether HA treatment activates these pathways in ovarian cancer cells and if specific inhibitors of these pathways can alter ovarian cancer sensitivity to carboplatin. This project will utilise a broad range of techniques including cell proliferation , western blotting,immunohistochemistry and qPCR.

Aim 1. Determine if HA activates AKT, ERK and Rho kinase pathways in ovarian cancer cell lines and primary cells established from ovarian cancer patients.

Aim 2. Determine if HA and specific kinase inhibitors can overcome platinum resistance in ovarian cancer cells.

PROJECT: Versican as a target to inhibit cancer metastasis.

Supervisors
Dr Carmela Ricciardelli
A/Prof Darryl Russell

Project Background

There is increasing evidence to suggest that extracellular matrix (ECM) components play an active role in tumour progression and metastasis. Proteoglycans are major components of the ECM and have been shown to regulate cell adhesion, cell signalling, apoptosis, migration and invasion. Increased expression of the chondroitin sulfate (CS) proteoglycan, versican in the peritumoral stromal matrix is associated with a poor outcome in many cancers, including breast and ovarian carcinoma.

Although there is the accumulating in vivo evidence that versican is pivotal in promoting cancer cell metastasis in different cancer types, the means of preventing actions of versican in carcinomas have not been explored. This study we will evaluate using in vitro and in vivo breast cancer models whether selective versican inhibition by versican siRNA, in addition to drugs known to inhibit versican synthesis; genistein, budesonide, formoterol and montelukast, can inhibit breast cancer invasive behaviour and block breast cancer metastasis. This project will utilise a broad range of techniques including using in vitro motility, adhesion and invasion assays and an in vivo animal model of breast cancer.

Aim 1. To assess the ability of pharmacological agents to inhibit versican synthesis and block invasive tumour cell behaviour *in vitro.*

Aim 2. To determine whether versican synthesis inhibitors reduce metastasis in in vivo cancer models

PROJECT: Role of ADAMTS1 and ADAMTS4 proteases in cancer metastasis.

Supervisors
A/Prof Darryl Russell
Dr Carmela Ricciardelli

Project Background

Metastatic spread to the lymph node and bone is the most significant cause of relapse and mortality in prostate cancer patients. The molecular processes which mediate metastasis of cancers to the bone have been a strong focus of recent research. The Adamts (adamalysin-thrombospondin) proteases are a family of metalloproteinases involved in extracellular matrix (ECM) processing. Adamts1 and Adamts4 are major bone matrix remodelling proteases. Substrates include versican a prominant stromal matrix component associated with breast

and prostate tumour progression. A recent report links Adamts1 to the bone metastatic gene signature. This project will focus on Adamts1 and 4 for which there growing evidence of a role in prostate cancer progression. This project will utilise a broad range of techniques using including immunohistochemistry, motility, adhesion and invasion assays and an *in vivo* animal model of prostate cancer.

Aim 1. To show that Adamts proteases promotes invasive migratory behaviour in prostate tumor cell lines in vitro.

Aim 2. To elucidate the association between Adamts1 or Adamts4 protein levels and metastatic disease in human prostate cancer and an in vivo mouse model.

References

- Ricciardelli C, Russell DL, Ween MP, Mayne K, Suwiwat S, Byers S, Marshall VR, Tilley WD, Horsfall DJ. Formation of hyaluronan- and versican-rich pericellular matrix by prostate cancer cells promotes cell motility. J Biol Chem 2007;282: 10814-25.
- Ricciardelli C, Oehler MK. Diverse molecular pathways in ovarian cancer and their clinical significance. Maturitas 2009;62: 270-5.
- Ricciardelli C, Sakko AJ, Ween MP, Russell DL, Horsfall DJ. The biological role and regulation of versican levels in cancer. Cancer Metastasis Rev 2009.
- Ween MP, Oehler MK, Ricciardelli C. Role of Versican, Hyaluronan and CD44 in Ovarian Cancer Metastasis. Int J Mol Sci 2011;12: 1009-29.
- Ween MP, Lokman NA, Hoffmann P, Rodgers RJ, Ricciardelli C, Oehler MK. Transforming growth factor-beta-induced protein secreted by peritoneal cells increases the

metastatic potential of ovarian cancer cells. Int J Cancer 2011;128: 1570-84.
- Ween MP, Oehler MK, Ricciardelli C. Transforming Growth Factor-Beta-Induced Protein (TGFBI)/(betaig-H3): A Matrix Protein with Dual Functions in Ovarian Cancer. Int J Mol Sci 2012;13: 10461-77.
- Lokman NA, Elder AS, Ricciardelli C, Oehler MK. Chick Chorioallantoic Membrane (CAM) Assay as an In Vivo Model to Study the Effect of Newly Identified Molecules on Ovarian Cancer Invasion and Metastasis. Int J Mol Sci 2012;13: 9959-70.
- Ween MP, Hummitzsch K, Rodgers RJ, Oehler MK, Ricciardelli C. Versican induces a pro-metastatic ovarian cancer cell behavior which can be inhibited by small hyaluronan oligosaccharides. Clin Exp Metastasis 2011;28: 113-25.
- Tan I de A, Ricciardelli C, Russell DL. The metalloproteinase ADAMTS1: a comprehensive review of its role in tumorigenic and metastatic pathways. Int J Cancer 2013;133: 2263-76.
- Ricciardelli C, Ween MP, Lokman NA, Tan IA, Pyragius CE, Oehler MK. Chemotherapy-induced hyaluronan production: a novel chemoresistance mechanism in ovarian cancer. BMC Cancer 2013;13: 476.
- Ricciardelli C, Frewin KM, Tan I de A, Williams ED, Opeskin K, Pritchard MA, Ingman WV, Russell DL. The ADAMTS1 protease gene is required for mammary tumor growth and metastasis. Am J Pathol 2011;179: 3075-85.
- Lokman NAW, M.P.; Oehler, M.K.; Ricciardelli, C. The role of annexin A2 in tumorigenesis and cancer progression. Cancer Microenvironment 2011.
- Lokman NA, Elder AS, Ween MP, Pyragius CE, Hoffmann P, Oehler MK, Ricciardelli C. Annexin A2 is regulated by ovarian cancer-peritoneal cell interactions and promotes metastasis. Oncotarget 2013;4: 1199-211.

Reproductive Endocrinology Group

Supervisors

Dr Louise Hull

Location: Medical School

Contact Person
Louise Hull
Phone: 0403 9933312
louise.hull@adelaide.edu.au

PROJECT: Endometriosis

Project Background

Endometriosis is another common condition in young women and its diagnosis and aetiology is uncertain. Dr Hull has pioneered new methods for diagnosis and treatment and uses cutting edge technology in her research group. Opportunity exists for medical students to combine patient interaction with high quality laboratory methods in her group.

Reproductive Immunology Group

Supervisors

Professor Sarah Robertson
Dr David Sharkey
Dr John Schjenken

Location: Medical School

Contact Person:
Professor Sarah Robertson
Phone: 8313 4094
sarah.robertson@adelaide.edu.au

Sarah Robertson is a NHMRC Principal Research Fellow and Head of the Reproductive Immunology group in the Research Centre for Reproductive Health. Her research focus is early pregnancy, particularly the cytokine biology and immunology of the uterus and early embryo development. Her team is made up of 6 postdocs and 5 postgraduate students, who work together to explore the importance of the peri-conceptual immune environment in optimal embryo implantation and placental development, and programming fetal development and health after birth.

Research in the Reproductive Immunology group centres on three related themes:

- The impact of the maternal immune response on success and quality of embryo implantation and reproductive outcome.
- Male seminal fluid signaling in the female reproductive tract and significance for inducing maternal adaptation for pregnancy, and healthy fetal development.
- The roles of cytokines and leukocytes and their micro-RNA regulatory pathways in the events of embryo development during early pregnancy.
- Inflammatory pathways in the events of parturition and preterm labour.

We seek to unravel the immune and cytokine networks of early pregnancy to understand how maternal immune tolerance to pregnancy is established, and how failure in this process contributes to infertility, miscarriage and pathologies of pregnancy in women. Our work also has applications in animal breeding industries where early pregnancy loss is a significant constraint.

Keywords: immunology, cytokines, uterus, embryo, pregnancy

PROJECT: The role of mir-146a during the peri-conceptional period of pregnancy

Theme title: Pregnancy immunology

Supervisors
Prof Sarah Robertson
Dr John Schjenken
Dr David Sharkey

Project Background

At the time of conception, male seminal fluid has a key role in interacting with epithelial cells lining the female reproductive tract to establish the environment conducive to pregnancy. Seminal fluid interacts with the female reproductive tract to induce pro-inflammatory cytokines and chemokines, in an inflammation-like response that initiates the maternal immune adaptations required for tolerance of paternal antigens and pregnancy success. Both the sperm and seminal plasma portions of the ejaculate have been shown to contribute to these changes. Various bioactive molecules regulate the progression and quality of this response, potentially including microRNAs (miRNA). miRNA are small non-coding RNAs (21-25 nucleotides in length) which function to down-regulate target expression. Our studies have recently identified that an important immune-regulatory miRNA, miR-146a is induced by sperm following coitus and may be regulating a number of targets important in the seminal fluid signalling response. This project will utilise miR-146a deficient mice to determine the role that miR-146a plays during the peri-conceptional period and throughout pregnancy. Techniques which will be used will be quantitative miRNA assays to determine miRNA expression, quantitative PCR and luminex to examine miR-146a targets as well as cytokine and chemokine expression and immunohistochemistry to examine immune cell subtypes. Pregnancy outcomes will also be measured from miR-146a deficient mice. This study will help us understand the role that miRNAs

play in the regulation of the inflammatory response during early pregnancy.

PROJECT: The role of mir-155 during the peri-conceptional period of pregnancy

Theme title: Pregnancy immunology

Supervisors
Prof Sarah Robertson
Dr John Schjenken
Dr David Sharkey

Project Background

An inflammatory response and subsequent immune adaptation occurs in the female reproductive tract after conception, to generate tolerance of paternal antigens and allow embryo implantation. In particular, T regulatory (Treg) cells play an integral role in these events. The molecular and cellular character of the inflammatory response, including the kinetics of its progression and resolution, are critical to Treg cell generation and implantation success. Various bioactive molecules regulate this inflammatory response, including microRNAs (miRNA). miRNA are small non-coding RNAs (21-25 nucleotides in length) which function to down-regulate target expression. Our studies have recently identified that an important Treg cell miRNA, miR-155 is induced following coitus and may play an important role in the generation of Treg cells required for immune tolerance. This project will utilise miR-155 deficient mice to determine the role that miR-155 plays during the peri-conceptional period and throughout pregnancy. Techniques which will be used will be quantitative miRNA assays to determine miRNA expression, quantitative PCR and luminex to examine miR-155 targets as well as cytokine and chemokine expression and immunohistochemistry to examine immune cell subtypes. Pregnancy outcomes will also be measured from miR-155 deficient mice. This study will help us understand the role that miRNAs play in the regulation of the inflammatory response during early pregnancy.

Keywords: microRNA / conception / immunology / inflammation / pregnancy

PROJECT: Novel toll-like receptor mechanisms of sperm signalling in the female reproductive tract

Theme title: Pregnancy immunology

Supervisors
Prof Sarah Robertson
Dr John Schjenken
Dr David Sharkey

Project Background

When seminal fluid is delivered into the female reproductive tract at coitus, it interacts with epithelial cells lining the cervix and uterus to induce pro-inflammatory cytokines and chemokines. This inflammation-like response initiates the maternal immune adaptations required for tolerance of paternal antigens and pregnancy progression. In addition to seminal plasma, our studies have recently shown that sperm play an important role in signalling to the female tissues. However, we are yet to identify the specific mechanism that sperm utilises to induce these changes. Using bioinformatics analysis of mouse endometrial microarray data, we have been able to predict signalling pathways utilised by sperm, including members of the Toll-Like Receptor Signalling Pathways. This project will employ mice with null mutations in key TLR signalling molecules, including TLR4KO and MyD88KO null mutant mice, to identify the role that TLR signalling pathways play in sperm signalling. Techniques which will be used include quantitative PCR and luminex analysis to identify cytokine and chemokine expression and immunohistochemistry to examine immune cell sub-types. The project will also utilize in vitro models of male-female signalling, involving human cervical cell lines. Quantitative RT-PCR and cytokine immunoassay will be used to characterise cervical cell responsiveness to male factor regulation. The findings from this study will help us understand the induction phase of the maternal immune response that allows successful pregnancy and may help us understand why some men have reduced fertility despite apparently normal sperm parameters.

Keywords: microRNA/ conception/ immunology/ inflammation/ pregnancy

PROJECT: T-regulatory (treg) cell stability and plasticity in immune tolerance during early pregnancy

Theme title: Pregnancy immunology

Supervisor
Prof Sarah Robertson

Project Background

To allow embryo implantation and successful pregnancy, the maternal immune system must become 'tolerant' to paternal transplantation antigens. Treg cells are now implicated as key cells mediating maternal immune tolerance. Discoveries in our laboratory show that semen plays an important role in establishing functional tolerance to male transplantation antigens during early pregnancy. We now seek to investigate the role of seminal factors in activating and expanding Treg cells in preparation for embryo implantation. The aim of this project is to investigate in mice the molecular events involved in activating Treg cells after mating. In particular the importance of seminal plasma TGFbeta and the role of male MHC antigens in semen will be investigated. The project will employ cytokine null mutant mouse models, linked with state-of-the-art digital flow cytometry (FACS), and quantitative RT-PCR for the Treg fate-determining transcription factor *Foxp3*. The findings will help us understand the induction phase of the maternal immune response permitting successful pregnancy, and have broader relevance

to the transmission of STDs and immune-mediated pathologies linked with infertility.

Keywords: Immunology/ T regulatory cells/ pregnancy

PROJECT: Macrophage regulation of implantation and placental development

Theme title: Embryo implantation

Supervisors
Prof Sarah Robertson
Prof Claire Roberts

Project Background

Macrophages are abundant within the uterus at implantation. Through their secretory products, macrophages are thought to be involved in the immune adaptations and tissue remodelling required for embryo implantation and placental development. To determine the impact of macrophage ablation during early pregnancy, this project will utilise CD11b-DTR transgenic mice to elicit transient systemic ablation of macrophages by administration of low dose diphtheria toxin (DT). The effects of macrophage ablation during the peri-implantation and post-implantation phases of pregnancy will be evaluated. In particular, the project will focus on the roles of macrophages in uterine vascular changes and development of the maternal vascular supply that is required for optimal placental growth and function. To determine whether tissue-remodelling and/or immune pathways are involved, different syngeneic and allogeneic mating combinations will be used. The project will use a range of experimental strategies including quantitative RT-PCR for gene expression analysis, fluorescent histochemistry, flow cytometry (FACS). The findings will help us understand the importance of macrophages in establishing receptivity of the endometrium to embryo implantation, and in particular their relationship to robust placental development. We believe that disruptions in this pathway are linked with pathologies of pregnancy such as preeclampsia, which is a major cause of poor fetal growth and problems in early post-natal life.

Keywords: macrophages / implantation / tolerance / angiogenesis / placenta

PROJECT: Macrophage regulation of preterm birth

Theme title: Embryo development

Supervisors
Prof Sarah Robertson
Dr Loretta Chin

Project Background

Macrophages are present in large numbers in the gestational tissues throughout the course of pregnancy and are prominent around the time of birth, as well as in preterm bitrth (<34 weeks gestation). Macrophages are implicated in critical roles in the timing of delivery, their precocious activation may be a central event in infection-induced preterm delivery. Our recent studies suggest that so-called 'M2' macrophages exert potent anti-inflammatory and immune suppressive functions in the gestational tissues, where they prevent inflammation to maintain quiescense of the maternal immune response and sustain pregnancy until term. To investigate the roles of macrophages during late gestation pregnancy, this project will utilise CD11b-DTR transgenic mice to elicit transient systemic ablation of macrophages by administration of low dose diphtheria toxin (DT). The effects of macrophage ablation during late gestation on the incidence of preterm delivery, as well as the underlying mechanistic pathways, will be evaluated. In particular, the project will focus on the roles of M2 macrophages in sustaining Treg cell populations and preventing NK cell and Th17 cell activation. The project will use a range of experimental strategies including quantitative RT-PCR for gene expression analysis, fluorescent histochemistry and flow cytometry (FACS). The findings will help us understand the importance of macrophages in controlling the timing of birth and in particular their relationship to susceptibility to preterm birth. Disruptions in M2 macrophages may be linked with the very high incidence of preterm birth in Western and developing countries (9-12% of all births) which is the most common cause of post-natal morbidity and mortality, as well as having life-long consequences in children born too soon.

Keywords: macrophages / pregnancy / preterm delivery

PROJECT: MHC disparity and placental vascular supply

Theme title: Pregnancy immunology

Supervisor
Prof Sarah Robertson
Prof Claire Roberts

MHC disparity between paternal and maternal genomes in pregnancy is beneficial to fetal growth and pregnancy success. This is linked with activation and expansion of maternal T cell populations which in a healthy pregnancy, are skewed towards T regulatory cells and immune toleerance. As well as inhibiting cytotoxic immunity towards the conceptus tissue, these T cells may help to promote placental development and robust access to the maternal blood supply. To investigate the role of T cells in placental development and transformation of maternal decidual vessels, this project will utilise wild-type and lymphocyte-deficient (scid) balb/c females, mated with congenic Balb/c and Balb/B mice to provide syngeneic and allogenic pregnancies respectively. The effects of T cell deficiency will be determined by comparing placental development and other reproductive parameters in pregnancies of the wild-type

(lymphocyte intact) versus scid (lymphocyte-deficient) females. Additionally we will use 'DEREG' mice which allow acute ablation of regulatory T cells to determine the contribution of Treg cells to placental vascular development. The project will employ a range of experimental strategies including immunohistochemistry and tissue morphometry to analyse placental vascular structure and physical interactions between endothelial cells and T cells, and quantitative RT-PCR for analysis of genes involved in vascular regulation. The results will provide new insight on the importance of T cells in the vascular adaptation required for optimal placental development and fetal growth. Problems with immune-regulated placental development underpin many common disorders of pregnancy including miscarriage, preeclampsia and poor fetal growth.

Keywords: T cells / pregnancy / placenta / vascular supply

Discipline of Paediatrics

- Women's and Children's Hospital
- Lyell McEwin Hospital
- Royal Adelaide Hospital
- South Australian Health and Medical Research Institute

"The Discipline of Paediatrics is located at the Women's and Children's Hospital, and includes the Vaccinology and Immunology Research Trials Unit. Honours projects in Paediatrics are also supervised by our multiple affiliates including members of other hospital departments and researchers in the Children's Research Centre. The Discipline has a wide range of clinical expertise and a strong commitment to clinical service in the Division of Paediatric Medicine at the Children, Youth and Women's Health Service. Our clinical staff provide services in multiple fields, including diabetes, endocrinology, gastroenterology, pulmonary medicine, sleep medicine, immunology, rheumatology, allergy and child & adolescent psychiatry."

Professor Jenny Couper
Head of Discipline of Paediatrics

Child Nutrition Research Centre (CNRC)



Supervisors
Professor Maria Makrides
Professor Robert Gibson
Dr Jo Zhou

Location: Women's and Children's Hospital, Flinders Medical Centre and Foodplus Research Centre

The overall aim of the Child Nutrition Research Centre is to optimise the nutritional intake of mothers and their infants, whether the infants are born preterm or at term. The rationale for our research is that improvements in nutritional status will optimise the growth, neurological development and immune system of all infants. Reducing susceptibility to allergy and associated diseases will have beneficial effects on infant quality of life as well as on whole-of-life health care costs.

PROJECT: Measurement of energy metabolites in dried blood spots.

Supervisors:
Prof Robert Gibson
Prof Maria Makrides
http://www.adelaide.edu.au/foodplus/
http://www.wchri.com.au/

Contact Person:
Prof Robert Gibson
robert.gibson@adelaide.edu.au.
Please use the subject heading 'Honours Project'.

Project Background

Assessing the nutritional status of preterm infants is of vital importance to evaluating their overall health. In human trials, blood sample analysis is an integral part of assessing physiological and immune function in participants. This blood collection is invasive and analysis involves using volumes of blood, which are not possible to obtain from new born infants. We have developed a new system that is based on analysis of a single drop of capillary blood collected by a finger/heel prick on to a piece of filter paper and dried. In this project we will aim to develop and validate a method of assessing a range of nutrients that are important to good health in dried blood spot samples.

This project will ideally suit an enthusiastic student who is interested in learning more about nutrition and the development of assays for detecting biomarkers for assessing nutrient status.

Techniques/Skills Learnt

- Scientific writing & literature review
- General laboratory techniques
- Chemical extraction
- Tandem mass spectrometry
- High performance liquid chromatography

Key References

- Jones DP, Park Y, Ziegler TR. Nutritional Metabolomics: Progress in Addressing Complexity in Diet and Health. Ann Rev Nutr. 2012 Apr 23.
- Skogstrand *et.al*. Effects of blood sample handling procedure on measurable inflammatory markers in plasma, serum, and dried blood spot samples. J Immunol Methods 336(2008) 78-84

PROJECT: Influence of maternal diet on the concentration of micronutrient elements in breast milk.

Supervisors
Dr Jo Zhou
Prof Robert Gibson

Contact Person:
Prof Robert Gibson
robert.gibson@adelaide.edu.au.
Please use the subject heading 'Honours Project'.

Project Background

Micronutrients such as iron, zinc and selenium are important for many aspects of development, growth and metabolism. Breast milk is the sole source of dietary micronutrients for exclusively breastfed infants. The aim of this study is to examine the influence of maternal diet during pregnancy and lactation on breast milk elemental micronutrient concentrations.

Techniques/Skills Learnt

- Scientific writing & literature review
- Dietary intake assessment
- General laboratory technique
- Elemental analysis of breast milk with ICPMS

Key References

- WHO (2001) Iron deficiency anaemia: assessment, prevention and control - A guide for programme managers.
- Siimes, et al. Breast milk iron--a declining concentration during the course of lactation. Acta Paediatr Scand 1979; 68:29

PROJECT: Iodine content of bread after mandatory iodine fortification.

Supervisors
Dr Jo Zhou
Prof Robert Gibson

Contact Person
Prof Robert Gibson
robert.gibson@adelaide.edu.au.
Please use the subject heading 'Honours Project'.

Project Background

Iodine is essential for thyroid hormone production, which in turn is important for normal growth and development. However, iodine deficiency has recently re-emerged in Australia. As a result, the government introduced mandatory iodine fortification by replacement of non-iodised salt with iodised salt in commercial bread making as a public health measure The aim of the study is to assess iodine content of different brands and types of breads in the supermarket.

Techniques/Skills Learnt

- Scientific writing & literature review
- General laboratory technique
- Analysis of iodine content in foods using ICPMS

Key References

- Food Standards Australia and New Zealand (2008) Proposal P1003 Mandatory iodine fortification for Australia assessment report.
- Australian Population Health Development Principal Committee (APHDPC) (2007) The Prevalence and Severity of Iodine Deficiency in Australia.

PROJECT: Measurement of vitamins A, D and E in dried blood spots.

Supervisors
Prof Robert Gibson
Dr Jo Zhou
http://www.adelaide.edu.au/foodplus/

Contact Person
Prof Robert Gibson
robert.gibson@adelaide.edu.au.

Project Background

Assessing the nutritional status of humans and animals is of vital importance to evaluating overall health. In both animal and human trials, blood sample analysis is an integral part of assessing physiological and immune function in participants. This blood collection is invasive and analysis involves using volumes of blood, which are not possible to obtain from some animals and new born infants. We have developed a new system that is based on analysis of a single drop of capillary blood collected by a finger/heel prick on to a piece of filter paper and dried. In this project we will aim to develop and validate a method of assessing the fat soluble vitamins that are important to good health in dried blood spot samples.

This project will ideally suit an enthusiastic student who is interested in learning more about nutrition and the development of assays for detecting biomarkers for assessing nutrient status.

Techniques/Skills Learnt

- Scientific writing and literature reviews
- Basic laboratory techniques
- Chemical extraction
- Gas chromatography
- High performance liquid chromatography

Key References

- Santos J, Mendiola JA, Oliveira MB, Ibáñez E, Herrero M. Sequential determination of fat- and water-soluble vitamins in green leafy vegetables during storage. J Chromatogr A. 2012 May 3.
- Thomas JB, Sharpless KE, Yen JH, Rimmer CA. Determination of fat-soluble vitamins and carotenoids in standard reference material 3280 multivitamin/multielement tablets by liquid chromatography with absorbance detection. J AOAC Int. 2011 May-Jun;94(3):815-22.
- Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Pérez-Sacristán B. Suitability of ultra-high performance liquid chromatography for the determination of fat-soluble nutritional status (vitamins A, E, D, and individual carotenoids). Anal Bioanal Chem. 2010 Jun;397(3):1389-93.

PROJECT: Measurement of nutrients in breast milk.

Supervisors
Prof Robert Gibson
Dr Jo Zhou
http://www.adelaide.edu.au/foodplus/

Contact Person
Prof Robert Gibson
robert.gibson@adelaide.edu.au.

Project Background

Assessing the nutritional status of humans and animals is of vital importance to evaluating overall health. In both animal and human studies, assessing the nutrient level in breast milk of dams/mothers is vital for an understanding of the nutrients that pups/babies receive. Currently there is no method to easily measure the nutrients in breast milk. We have developed a new system that is based on analysis of a single drop of breast milk on to a piece of filter paper and dried. Sections of the dried milk spot can then be analysed by mass spectrometry. In this

project we will aim to develop and validate a method of assessing a range of nutrients that are important to good health of infants.

This project will ideally suit an enthusiastic student who is interested in learning more about nutrition and the development of assays for detecting biomarkers for assessing nutrient status.

Techniques/Skills Learnt

- Scientific writing & literature review
- Dietary intake assessment
- General laboratory techniques
- Analysis of breast milk nutrient levels
- Mass spectroscopy

Key References

- Jones DP, Park Y, Ziegler TR. Nutritional Metabolomics: Progress in Addressing Complexity in Diet and Health. Ann Rev Nutr. 2012 Apr 23.
- Mäkelä J, Linderborg K, Niinikoski H, Yang B, Lagström H. Breast milk fatty acid composition differs between overweight and normal weight women: the STEPS Study. Eur J Nutr. 2012 May 26.
- Hoppu U, Isolauri E, Laakso P, Matomäki J, Laitinen K. Probiotics and dietary counselling targeting maternal dietary fat intake modifies breast milk fatty acids and cytokines. Eur J Nutr. 2012 Mar;51(2):211-9.

Scholarships available and are awarded principally on academic merit.

Craniofacial Research Group


Supervisors
Associate Professor Barry Powell
Professor Peter Anderson

Women's and Children's Health Research Institute at the Women's and Children's Hospital, North Adelaide.

Contact Person
Associate Professor Barry Powell
8161 7652
barry.powell@adelaide.edu.au

We study molecular processes in a developmental disorder that affects growth and cognition in children. Through our research on craniosynostosis, a craniofacial abnormality with genetic and non-genetic influences and an incidence of 1 in 2500 births, we discovered several genes with novel functions in bone development (Coussens et al., 2007; Leitch et al., 2013). Our research is aimed at understanding what they do and applying that knowledge to develop new treatments for bone pathologies in collaboration with clinicians. Recently, we discovered that the proteoglycans, glypican 1 and glypican 3 (GPC1 and GPC3) act together in skull cells to regulate activity of the key bone growth factor, bone morphogenetic protein 2 (Dwivedi et al., 2013a). Gpc1 and Gpc3 are co-regulators of major growth factor pathways, notably BMP, FGF, Hedgehog and Wnt (Dwivedi et al., 2013b) and therefore can impact on diverse developmental mechanisms. To study their cooperative function, we have now made a double gene knockout model. The Honours projects will investigate interesting features of that model.

PROJECT: Role of Gpc1 and Gpc3 in development and impact on BMP, FGF, Hedgehog and Wnt signalling

Project Background

The Honours projects will investigate the impact of Gpc1 and Gpc3 on development, with a focus on the craniofacial complex and particular organs. Specialized phenotypic characterization of the double gene knockout will be carried out in conjunction with an investigation of the impact of Gpc1 and Gpc3 on the activity of the BMP, FGF, Hedgehog and Wnt pathways in organ development and function. This research is expected to provide new insight into how these pathways are controlled and how that impacts on development. It may also contribute to a publication on the model. In the laboratory, students will gain expertise in core molecular cell biology techniques, microscopy and animal handling.

References:

- Coussens AK, CR Wilkinson, IP Hughes, CP Morris, A van Daal, PJ Anderson and BC Powell. 2007. Unravelling the molecular control of calvarial suture morphogenesis in children with craniosynostosis. *BMC Genomics*. 8:doi: 10.1186/1471-2164-8-458.
- Dwivedi, PP, Grose, RH, Filmus, J, Hii, CST, Xian, CJ, Anderson, PJ and Powell, BC. 2013a. Regulation of bone morphogenetic protein signalling and cranial osteogenesis by Gpc1 and Gpc3. Bone 55:367-376.
- Dwivedi, PP, Lam, NN and Powell, BC. 2013b. Boning up on glypicans - opportunities for new insights into bone biology. Cell Biochemistry & Function 31:91-114.
- Leitch, VD, Dwivedi, PP, Anderson, PJ and Powell, BC. 2013. Retinol-binding protein 4 downregulation during osteogenesis and its localization to non-endocytic vesicles in human cranial suture mesenchymal cells suggest a novel tissue function. Histochem Cell Biol 139:75-87.

These projects are eligible for the WCHRI Honours Scholarship of $2,000.

See the website for further details and how to apply or contact Barry Powell
http://www.wchri.com.au/Scholarships.htm

Cystic Fibrosis Research Group

Supervisors:

A/Prof David Parsons
Dr Martin Donnelley
Dr Patricia Cmielewski
Dr Nigel Farrow
Dr Chantelle McIntyre

From Left to Right

(L-R) Dr Nigel Farrow, Harsha Padmanabhan, Dr Trish Cmielewski, A/Prof David Parsons, Ali McCarron, Dr Chantelle McIntyre, Bernadette Boog, Dr Martin Donnelley, Dr Greg Smith. Absent: Ryan Green

Respiratory & Sleep Medicine / Alan Scott CF Research Laboratory
Gilbert Building, Women's & Children's Hospital, North Adelaide

Contacts
Associate Professor David Parsons
08 8161 7004
david.parsons@health.sa.gov.au
http://www.adelaide.edu.au/robinson-research-institute/researchers/group-leaders/parsons/
Dr Martin Donnelley
martin.donnelley@adelaide.edu.au

Lung disease is the primary cause of worsening health problems in young people with CF. It greatly affects their quality of life and is the overwhelming cause of early death. Our group is developing an effective treatment and potentially a life-long correction for the airway disease of Cystic Fibrosis (CF).

Our research utilises a lentiviral (LV) vector delivery system to study how to produce safe and effective gene delivery into airway cells in animal models. We use reporter genes such as LacZ, luciferase, GFP and eYFP, as well as the therapeutic CFTR gene. This involves a significant amount of molecular biology as well as work with lab animals.

Our work has included studies across mice, sheep and marmoset animal models, and we are planning to establish CF pig and ferret colonies in Adelaide to improve the testing of our genetic treatments for CF airway disease. Our approach especially targets airway stem cells in vivo, and in some mouse studies this approach has already produced up to lifetime gene expression after a single dose event.

Our new state-of-the-art research laboratory opened in 2012. Through the enthusiastic work of the Cure4CF Foundation Ltd (www.cure4cf.org), and substantial completion funding provided by the WCH Foundation, the Alan Scott CF research laboratory is now in place in the Gilbert Building at the WCH. This laboratory is used for plasmid and viral vector production, molecular assays and histological processing, and a range of bench and computer-based development work for developing testing and measuring the effects of our gene and cell therapies in vivo.

PROJECT 1: Investigating the differentiating and self-proliferating potential of endogenous respiratory stem cells lacking the CFTR protein

Project Background

A recent study by our research team has revealed significantly more airway stem cells are present in cystic fibrosis (CF) mouse airways. We also have pilot data showing that airway remodelling of mucus secreting goblet cells occurs, with more present in CF mice compared to the same regions in normal mice. It is unclear if the goblet cell remodelling is due to the larger numbers of stem cells. This exciting project will investigate this relationship further, utilising flow cytometric cell sorting (FACS) to isolate respiratory airway stem cells from both CF transgenic and normal mice, and clonal-growth assays to evaluate the levels of differentiating and self-proliferating potential of respiratory stem cells when CF channels are not present (in CF mice). We propose to also test our-well established gene therapy technique, to restore CF function in the respiratory stem cells in CF transgenic mice where the CF gene is entirely absent from the airways. This will allow us to determine if

there are differences in differentiating cells and/or the self-proliferating potential of the airway epithelium that can be corrected using our gene therapy protocol.

PROJECT 2: Can vector re-dosing improve gene expression levels?

Project Background

In order to provide lifelong therapeutic gene expression it may be beneficial or necessary to produce higher levels of initial gene expression through initial multi-dosing (since this may be more effective than a single initial dose), but also to be able to repeat-dose if gene expression wanes over time. Few studies have examined the potential for re-administration of LV vectors to the airways.

LV proteins are considered less immunogenic than other viral vectors, although other components of the vector preparation may be capable of inducing an immune response. We have recently altered our LV production methods to utilize plasmid removal treatment and serum-free culture, and hypothesize that these vector production modifications will reduce the immunogenicity of the delivered vector preparation, improving the success of repeat administration.

The overall aim of this project is to determine the most effective short-term multi-dosing of our clinically-relevant LV vector to increase initial levels of gene expression, compared to our standard single dose protocol, and to examine whether repeat-dosing at later time-point(s) can sustain expression levels avoiding waning gene expression due to natural cell turnover.

This Honours project will involve plasmid and vector production, animal handling, and molecular analyses to answer key components of the overall study.

PROJECT 3: Is LPC airway pre-treatment safe to use for enhancement of gene expression in airway gene transfer procedures?

Our group has developed a proven gene transfer method that involves a pre-conditioning of the airway surface using the compound LPC, which is thought to open tight junctions between cells allowing vector access to the basolateral membrane. Importantly, we have shown that LPC use greatly enhances airway gene transduction, in the usual test location of the nasal airways. Although we have never seen adverse effects from this pre-treatment in 'healthy' mouse lungs, there is some concern that opening tight junctions in a CF lung already infected with bacterial pathogens might increase the risk of systemic infection.
The aim of this project is to test whether LPC pre-treatment in a mouse model of lung infection has positive, neutral or negative effects on animal and lung health. This project will involve plasmid and vector production, Pseudomonas aeroginosa agar-bead production and delivery, animal handling (including non-surgical intubation) and molecular and histological analyses.

OTHER PROJECTS:

The proposed projects are sample of projects that are available. Should the project listed above not suit your particular interest please talk with us about other potential projects related to the creation of CF lung disease models, and assessment of treatments for CF airway disease, as we may be able to tailor a project to your specific areas of interest.

Lysosomal Diseases Research Unit, Neurobiology Section

Supervisor/Contact Person
Dr Tim Sargeant
Head, Neurobiology Section
Telephone: 8128 4940
Email: tim.sargeant@sahmri.com

Location: South Australian Health and Medical Research Institute, North Terrace

The Lysosomal Diseases Research Unit is a large, well-established, multidisciplinary team of scientists, research assistants and students, and is a world leader in lysosomal disorder research. The Unit has been extremely successful at both basic science and translating this to successful clinical and commercial outcomes.

The Neurobiology Section is investigating how the lysosomal network interacts with late-onset neurodegenerative conditions such as Alzheimer's disease. The lysosomal network is the recycling centre of the cell and is critically important for long-lived, terminally-differentiated neurons. As part of this role, the lysosomal network is required for efficient degradation of dementia-related proteins. The aim of our research is to exploit the lysosomal system for mechanisms of therapeutic potential in late-onset neurodegenerative disease.

Project: Quantification of Alzheimer's disease-related peptide amyloid-β using mass spectrometry

Project Background

Late-onset Alzheimer's disease is the most common cause of dementia and treatment of this condition is the largest unmet need in neurology. Amyloid plaques that form in regions of the brain such as the cerebral cortex and hippocampus constitute one of the hallmarks of this progressive neurodegenerative disease. These plaques are formed from a peptide fragment of the amyloid precursor protein, called amyloid-β. Degradation of this peptide is known to be perturbed in Late-onset Alzheimer's disease. Our research group aims to investigate how genetic heterogeneity influences degradation of amyloid-β within neurons.

To assist in this goal, an honours degree candidate will develop a mass spectrometry-based method to detect and quantify amyloid-β. The candidate will develop optimum sample preparation techniques and utilise two different mass spectrometers to determine which is most suitable for this experiment. Through this project the candidate will gain experience in practical laboratory skills, experimental design and the use of sophisticated laboratory equipment. For exceptional students, this project has scope to include analysis of innovative cell models of Alzheimer's disease. The successful applicant will interact with Dr Tim Sargeant, Dr Marten Snel (Head, Mass Spectrometry) and Dr Paul Trim (Research Officer, Mass Spectrometry).

Project: Analysis of degradation of the Alzheimer's disease-related peptide amyloid-β

Project Background

Late onset Alzheimer's disease is the leading cause of dementia, a condition that will afflict over half a million people in Australia by the year 2050. There is currently no effective treatment for this progressive neurodegenerative disease and a greater understanding of pathogenesis is urgently required. A key pathological process in Alzheimer's disease is generation of amyloid-β, a peptide fragment of the amyloid precursor protein that forms hallmark amyloid plaques in central nervous system tissue. Amyloid-β is degraded in the lysosome by a number of different cathepsin proteases, however, a direct comparison that determines the role of each of these important proteases has not been performed. An honours degree candidate will use cell models constructed using lentiviral gene delivery in conjunction with CRISPR/Cas9 genome editing to interrogate the role of cathepsin proteases in the degradation of amyloid-beta. Pharmacological methods of enzyme inhibition will also be used. The candidate will learn new genome editing techniques and skills valuable for in-vitro disease modelling and molecular biology.

References

Saido T, Leissring MA. Proteolytic degradation of amyloid β-protein. Cold Spring Harb Perspect Med. 2012 Jun;2(6):a006379.

Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science. 2010 Dec 24;330(6012):1774.

Matrix Biology Unit


Supervisors

Dr Sharon Byers
Dr Ainslie Derrick-Roberts

Location: Women's and Children's Hospital

Contacts

Dr Sharon Byers
Phone: 8161 7093
sharon.byers@adelaide.edu.au

Dr Ainslie Derrick-Roberts
Phone: 8161 6373
ainslie.derrickroberts@adelaide.edu.au

Our research interest lies in the regulation of a group of complex carbohydrates called glycosaminoglycans (gags). Gags are found in all tissues where they define tissue structure and modify tissue growth through the regulation of growth factor activity. They are constantly synthesised and degraded as part of normal development. Defects in degradation lead to the mucopolysaccharidosis (MPS) group of inherited metabolic disorders. Our laboratory is focused on the characterisation of disease progression and the development of safe and effective therapies for MPS children and played a key role in the commercialization of enzyme replacement therapy. The laboratory is situated in the department of Genetics and Molecular Pathology, SA Pathology (WCH site). The department is the Australasian centre for the diagnosis and treatment of children with MPS.

The multiple organs systems affected by the accumulation of undegraded gag in MPS presents a challenge to the clinical management of affected children. While somatic tissues such as liver and kidney are amenable to replacement therapies, the brain and the cartilage component of the musculoskeletal system are untreatable. Students will join ongoing projects in one of the following areas:-

Key Words:
Genetic disease, childhood disorders, therapy, murine models of disease, behavioural tests, bone growth

PROJECT: Targeting CNS pathology in MPS disorders

Project background:

CNS pathology that manifests as a severe, progressive loss of cognitive function is a major symptom of 8 of the 12 MPS types and is currently untreatable. The aim of this project is to find a way to treat CNS pathology in MPS disorders. Gene therapy replacement of the missing gene has shown promising results in mouse models (Anson et al., 2011), however has a limited effect on the CNS due to the presence of the blood-brain barrier. More recently, mesenchymal stem cells have been transduced with gene therapy vectors to overexpress lysosomal enzymes have been administered either systemically or locally within the brain to analyse their effect on MPS disease pathology. Both of these therapies can be used to target CNS disease in mouse models of MPS.

Students undertaking this project will learn fundamental research techniques applicable to a wide range of research areas. These include cell culture, small animal handling, PCR genotyping, behavioural testing (eg water maze tests), enzyme assay, electrophoresis and carbohydrate biochemistry. Equipment to be used will include: microscopes, centrifuges, electrophoresis equipment, fluorimeter, mass spectrometer and laminar flow/biohazard hoods.

References:

- Roberts ALK, Rees MH, Klebe S, Fletcher JM and Byers S. (2007): Improvement in behaviour after substrate deprivation therapy with rhodamine B in a mouse model of MPS IIIA. Molecular Genetics and Metabolism, 92: 115-121.
- Anson DS, McIntyre C, Byers S. (2011): Therapies for neurological disease in the mucopolysaccharidoses. Curr Gene Ther. 11: 132-43.
- Derrick-Roberts ALK, Ly M, Marais W and Byers S. (2012). Rhodamine B and 2-acetamido-1,3,6-tri-O-acetyl-4-deoxy-4-fluoro-D-glucopyranose (F-GlcNAc) inhibit chondroitin/dermatan and keratan sulphate synthesis by different mechanisms in bovine chondrocytes. Mol. Genet. Metab. 106: 214-20.

PROJECT: Understanding skeletal disease in MPS patients

Project background:

Direct injection of enzyme into the joint space increases the localized concentration of enzyme replacement therapy (ERT) and improves joint

outcome (Auclair *et al* 2006, 2007). We have recently shown that the same improvement can be achieved by a gene therapy approach to transduce joint cells (Byers *et al* 2009). In this project students will join an ongoing project to investigate the efficacy of systemic gene therapy alone or in combination with intra-articular gene therapy to prevent the development of both bone and joint pathology.

Short stature is a feature of 6 of the 12 PS disorders which leads to problems with mobility. Therapy options are limited and ERT available for some MPS disorders does not increase bone length in affected children even though it has a positive effect on other symptoms. This suggests that we need a better understanding of bone growth and by isolating distinct regions of the growth plate responsible for bone lengthening we can identify key markers involved in long bone growth which can be new targets to improve short stature. Characterisation of skeletal disease using micro-CT and histology will also provide an understanding of the mechanisms affected in bone growth in different MPS models.

Students undertaking this project will learn fundamental research techniques applicable to a wide range of research areas. These include small animal handling, bone histomorphometric techniques, micro CT, laser capture microdissection, real-time PCR, electrophoresis and carbohydrate biochemistry. Equipment to be used will include: microscopes, image analysis equipment, centrifuges, electrophoresis equipment, fluorimeter and laminar flow/biohazard hoods.

References:

- Macsai CE, Derrick-Roberts AL, *et al.* (2012): Skeletal response to lentiviral mediated gene therapy in a mouse model of MPS VII. Mol Genet Metab. 2012 Jun;106: 202-13
- Byers S, Rothe M, *et al.* (2009). Lentiviral mediated correction of MPS VI cells and gene transfer to skeletal tissues. *Molecular Genetics and Metabolism*, 97: 102-108.
- Auclair D, Hopwood JJ, *et al.* (2007): Intra-articular enzyme administration for joint disease in feline mucopolysaccharidosis VI: Long-term therapy. *Molecular Genetics and Metabolism,* 91: 352-61

Molecular Immunology

Supervisor

Associate Professor Simon Barry
Phone: 8161 6562
simon.barry@adelaide.edu.au

Location: Women's and Children's Hospital

Contact Persons
Dr Tim Sadlon
Phone: 8161 6729
timothy.sadlon@adelaide.edu.au

Dr Cheryl Brown
Phone: 8161 6729
cheryl.brown@adelaide.edu.au

My lab is interested in how a healthy immune system balances being ready to react by swiftly fighting off pathogens, while maintaining tolerance to harmless challenges such as food and body tissues. The cellular immune repertoire in humans is broad, but we are focussed on a T cell subset that is shaped along with the immune system from birth. These cells are known as regulatory T cells, and they are accepted as the policemen of the immune system. There is increasing evidence that in a wide number of disease states including autoimmune diseases such as Type 1 diabetes and Multiple Sclerosis, these cells fail to regulate the immune system, and allow inappropriate destruction of tissues that are essential for life. In order to understand how this breaks down in disease one must first understand what is the basis of a healthy Treg. To do this we are focussed on human cells and we use a number of state of the art gene discovery tools such as microarrays to identify and then confirm the key genes in Treg function. As Treg play a role in autoimmune disease, cancer and transplantation tolerance, our research findings have a wide clinical application. The projects below are from parts of this overall research program. We currently have 11 members of the research group, which provides lab and academic support for students.

PROJECT: Molecular identification of Regulatory T cells

Project Background

The recent identification of regulatory T cells (Tregs) as a key mediator of central and peripheral tolerance has led to an increase in our understanding of the cellular mechanisms by which humans maintains the healthy state. This has been confirmed by the identification of a transcription factor named FOXP3 in both mouse and human Tregs, which is proven to be essential for formation and function of the committed T cell subset that has regulatory capacity. There is however, very little known about the molecular basis of this process. This project aims to identify the genes directly regulated by FOXP3 and to determine their role in the regulatory phenotype. We have used a number of direct and indirect molecular approaches such as Chromatin Immunoprecipitation and microarray analysis to profile genes regulated by FOXP3 (Fig 1), and we will validate their role in regulatory function by direct assays and by over expression or gene ablation studies.

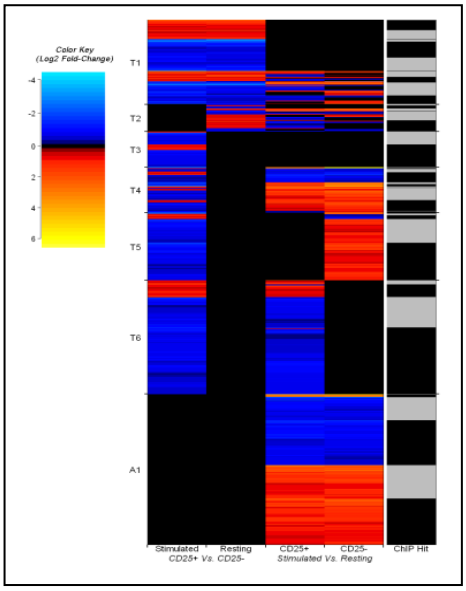


Fig 1: Comparative microarray analysis of CD4 CD25+ natural Treg to identify the key genes required for function.

The candidate genes identified in this approach may lead to therapeutic approaches for intervention in the function of regulatory cells, and will also have application for diagnostic analysis of regulatory cell function. Analysis of these and other Tcells from disease samples eg IBD (Fig 2) reveals the clinical

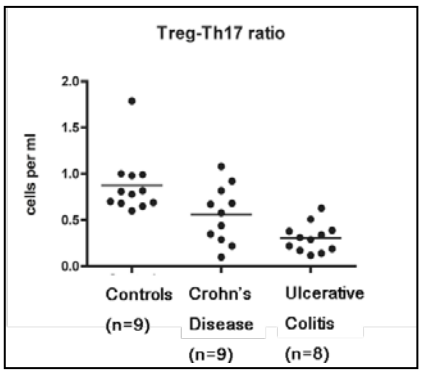


Fig 2: Comparative analysis of CD4 CD25+ natural Treg and Th17 in IBD patients shows a defect in the ratio of these cells.

defect in numbers of Treg.

Techniques/skills/approach

Molecular biology, RT PCR, microarray data analysis, tissue culture lentiviral production, gene silencing and over expression, functional assay.

References

- Bresatz S Sadlon T, Millard D, Zola H, Barry SC. Purification and characterization of CD4+ CD25+ regulatory cells from Cord and peripheral blood. J Immunuol Methods 2007;327:53-62. Impact Factor = 2.5, Journal rank in field 46/114
- Zola H, Swart B, Banham A, Barry SC, Beare A, Bensussan A, Boumsell L, D Buckley C, Buhring HJ, Clark G, Engel P, Fox D, Jin BQ, Macardle PJ, Malavasi F, Mason D, Stockinger H, Yang X. CD molecules 2006--human cell differentiation molecules. J Immunol Methods 2007;319(1-2):1-. Impact Factor = 2.5, Journal rank in field 46/114

PROJECT: Cord Blood Stem cell differentiation into regulatory T cells.

Project Background

The clinical application of regulatory T cells is significantly hampered by the limited cell numbers that can be obtained from either cord or adult blood. Attempts to expand these purified Treg *ex vivo* have shown some promise, but there is some evidence that after extended culture *ex vivo* these cells lose their suppressive capacity. An alternative approach is to generate large numbers of T cells *de novo* from stem cells since these cells have the capacity to differentiate into all cells of the haemopoietic system. We have established an *ex vivo* differentiation assay that can expand cord blood stem cells and induce their differentiation along the lymphoid pathway using a co-culture system giving notch signals via the Notch ligand Delta like 1 (Fig 3). In this system we robustly observe 5-600 fold expansion of cell numbers and the generation of T cell subsets as defined by CD4/CD8 staining.

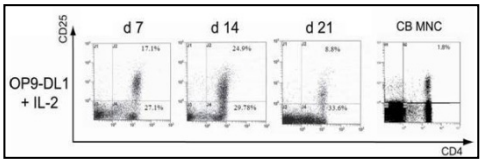


Fig 3. Cord blood stem cells on feeder cells showing formation of CD4 CD25+ subsets with similar characteristics to natural Treg

Techniques/skills/approach

Molecular biology, RT PCR, tissue culture, lentiviral production, gene silencing and over expression, functional assay with cord blood stem cells.

References

- Hutton JF, Gargett T, Sadlon TJ, Bresatz S, Brown CY, Zola H, Shannon MF, D'Andrea RJ, Barry SC: Development of CD4+CD25+FOXP3+ Regulatory T cells from Cord Blood Haemopoietic Progenitor Cells. Journal of Leukocyte Biology in press ePub Dec 22 08. Impact Factor = 4.3, Journal rank in field 50/156

PROJECT: Lentiviral vectors for gene delivery and gene ablation.

Project Background

Manipulation of primary cells has a key limitation in that these cells are refractory to standard transfection protocols. Also, since they are often of low mitotic index, they are only infected at low efficiency by murine retroviruses (RV), as these viruses require cell division for integration. The recent development of HIV1 based lentivectors (LV) provides an attractive option for gene delivery into T cell and stem cell populations, as these viruses carry the necessary cis elements to facilitate nuclear transport and integration in the absence of cell division. We have developed a suite of lentiviral vectors for stable gene delivery into primary cells both for gene therapy and gene discovery applications, and more recently for gene ablation using RNA interference (Fig 4). This technology relies on the expression of a short hairpin RNA structure that is complimentary to the gene target, and that is processed by cellular machinery to generate an RNA oligo that can bind to and target the mRNA for destruction.

Techniques/skills/approach

Molecular biology, RT PCR, Tissue culture, lentiviral production, gene silencing and over expression,

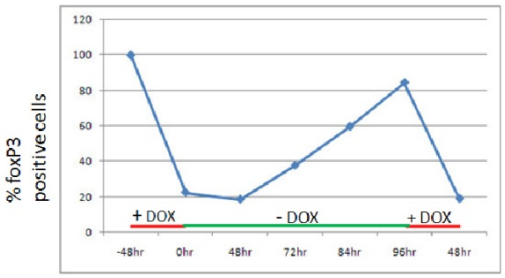


Fig 4. Lentiviral delivery of shRNAi showing abalation of FoxP3 expression that is inducible with doxicyclin and is reversible.

functional assay, T cell assays.

References

- Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, Khew-Goodall Y and Goodall GJ: The microRNA-200 family and miR-205 regulate epithelial-mesenchymal transition by targeting the E-cadherin repressors, ZEB1 and SIP1. Nature Cell Biology 2008 10 (5)593-601 Impact Factor F = 18.1, [28] J Journal rank in field 5/156
- Barry SC,Coates PT. Retroviral escape using DC - that's what Friends are for. Blood 2007 110(12)3819-3820 Impact Factor = 10.1, Journal rank in field 2/59
- Drabsch Y, Hugo H, Zhang R, Dowhan DH, Miao YR, Gewirtz AM, Barry, SC, Ramsay RG and Gonda TJ. Mechanism of and Requirement for Estrogen-Regulated MYB Expression in Estrogen Receptor-Positive Breast Cancer Cells. PNAS 2007;104(34):13762-7. Impact Factor = 10.9, Journal rank in field 3/45
- Brzezinski M, Yanay O, Waldron L, Barry SC and Osborne WRA. G-CSF-lentivirus provided long-term elevated neutrophil counts in rats and sequential EPO-lentivirus administration produced increased hematocrits in both lentivirus treated and naïve rats. J Gene Medicine 2007;9(7):571-8. Impact Factor = 4.8, Journal rank in field 8/75
- Barry SC Brezinzki M, Yanay O, Seppen, J Osborne WRA. Sustained elevation of neutrophils in rats induced by lentivirus-mediated G-CSF delivery. J Gene medicine 2005;7(12):1510-6. Impact Factor = 4.8, Journal rank in field 8/75

PROJECT: Is there a role for FOXP3 in Breast Cancer?

Project Background

There is very recent evidence that FOXP3 may also play a role in breast cancer as a new tumour suppressor. This means that its expression prevents the transformation leading to cancer, and in cells that have transformed it is no longer correctly expressed. As we have discovered a great many of the genes that are directly regulated by FOXP3 in Tregs, it is likely that some of these are also required for prevention of breast cancer. We have now confirmed that FOXP3 is expressed in healthy breast epithelial cells, and are testing a number of genes for their role in either the loss of normal FOXP3 expression, or the progression to cancer. This includes a number of micro RNAs that are controlled by FOXP3 (quantitated by RT PCR in Fig 5), one of which (mir21) has been confirmed to

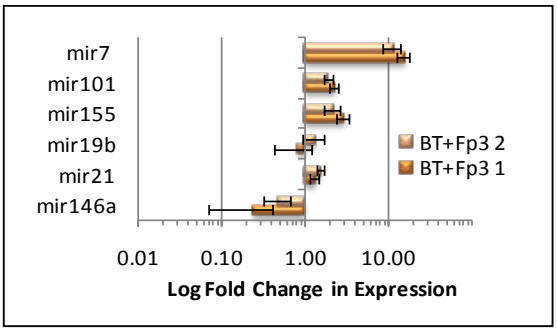


Fig 5: When FOXP3 is over expressed using a lentivirus in a breast cancer cell line, we observe increased expression of target micro RNAs.

play a role on breast cancer. We aim to demonstrate that correction of the FOXP3 expression defect can reverse these transformation causing genes and restore a healthy state.

Techniques/skills/approach

Molecular biology, RT PCR, microarray data analysis, tissue culture, lentiviral production, gene silencing and over expression, functional assay in breast cancer cells.

References

- Zuo, T., et al., FOXP3 is a novel transcriptional repressor for the breast cancer oncogene SKP2. The Journal of Clinical Investigation, 2007. 117(12): p. 3765-3773.
- Zuo, T., et al., FOXP3 is an x-linked breast cancer suppressor gene and an important repressor of the HER-2/ErbB2 oncogene. Cell, 2007. 129: p. 1275-1286.

Honours students are encouraged to continue on to PhD studies in my group.

Molecular Neurogenetics

Supervisors

Associate Professor Cheryl Shoubridge (pictured)
Dr Kristie Lee
Dr Matilda Jackson

Location: Level 2, Bragg Building

Contact Person

Associate Professor Cheryl Shoubridge
Phone: 8313 2355
cheryl.shoubridge@adelaide.edu.au

Identification of genes and understanding of molecular mechanisms leading to intellectual disabilities, autisms and some epilepsies represents a challenge of significant medical importance. Our research seeks to further our understanding of human brain function through the identification of genes and characterisation of their naturally occurring mutations implicated in various disorders of the brain. The Molecular Neurogenetics laboratory focuses on identifying the molecular mechanisms and functional impact of mutations in genes causing X-linked intellectual disability (XLID). The key areas of research include utilizing animal models and tissue culture assays to investigate the functional impact of patient mutations in genes involved in X-linked intellectual disability XLID, in particular the ARX and IQSEC2 genes.

We have mouse models to investigate functional impact of the two most frequent expanded polyalanine tract mutations in the ARX gene. Our ongoing work aims to establish the molecular mechanisms of disease associated with a range of expanded polyalanine tract mutations in ARX to begin to understand how these mutations underpin the intellectual disability with and without a broad spectrum of associated clinical symptoms in affected patients, including epilepsy. We are also interested in more fundamental aspects of ARX biology and are currently investigating how phosphorylation may regulate the function of the ARX homeodomain transcription factor.

Honours students are encouraged to remain with our research team to undertake a Ph.D.

PROJECT : Understanding the molecular impact of two common *Arx* polyalanine expansions mutations on pancreatic function and glucose homeostasis.

Project Background

Proper brain function relies on an orchestrated maturation and migration of diverse neuronal populations. When the function of the Aristaless related homeobox gene (ARX) is lost due to severe mutations, the capability of neuronal development is severely compromised. Patients with ARX loss-of-function mutations are afflicted with catastrophic brain malformations such as smooth brain (lissencephaly) or hydrocephaly (Shoubridge et al., 2010; Shoubridge et al., 2012). A less severe but more common type of mutation in ARX leads to expansion of polyalanine tracts. Despite a morphologically normal-looking brain, these patients display intellectual disability often in conjunction with seizures and other clinical features. We have mice that model the two most common human polyalanine tract expansions (Kitamura et al 2009; Lee et al 2014); with recent studies undertaken in our laboratory demonstrating that both mouse models present with myoclonic seizures during postnatal development. Large fluctuations in body weight were noted both pre- and post-seizure, which could be exacerbating or contributing to established seizure state. In addition to brain development, ARX is critical for the correct development of a major cell type in the pancreas (alpha-cell). The pancreas plays a major role in nutritional and glucose homeostasis, through the synthesis and regulation of hormones and enzymes, and is implicated in the disease progression of diabetes and obesity. The honours project will aim to identify changes in pancreatic cell fate, hormone regulation and glucose homeostasis due to two most common human polyalanine tract expansions. Techniques involved include; immunohistochemistry, immunofluorescence, RNA extraction, qRT-PCR, ELISA, mouse handling and monitoring.

Project . Investigating the pathogenic mechanisms of mutations in IQSEC2 in intellectual disability.

Project Background

IQSEC2 is a guanine nucleotide exchange factor

activating ARF proteins at membrane surfaces. Patients with mutations in *IQSEC2* frequently present with non-syndromic intellectual disability with particular deficits in language. We have shown that mutations located in the Sec7 and IQ-like domains of *IQSEC2* have been shown to affect the catalytic capacity of the protein activate Arfs (Shoubridge et al., Nature Genetics 2010). Since our original publication additional, novel, mutations have been reported clinically but with limited understanding of the pathogenic mechanisms impacting on IQSEC2 function. The honours project will establish the impact of these mutations on the function of the protein, including the enzymatic capacity to activate ARFs. The primary assay involves cDNA of wild-type IQSEC2 or IQSEC2 engineered with patient mutations overexpressed in cells in culture and the proteins incubated with ARFs. Using a protein-protein pulldown assay the level of activated ARFs is measured. Techniques involved will include DNA cloning, in vitro mutagenesis, general cell culture including transfection, immunoprecipitation, and protein analysis including Western blotting.

References

- Collombat P, Mansouri A, Hecksher-Sorensen J, Serup P, Krull J, Gradwohl G, Gruss P. Opposing actions of Arx and Pax4 in endocrine pancreas development. (2003) *Genes & Development,* 17, 2591-2603.
- Collombat P, Hecksher-Sorensen J, Broccoli V, Krull J, Ponte I, Mundiger T, Smith J, Gruss P, Serup P, Mansouri A. The simultaneous loss of Arx and Pax4 genes promote a somatostatin-producing cell fate specification at the expense of the a- and β-cell lineages in the mouse endocrine pancreas. (2005) *Development*, 132, 2969-2980.
- Kitamura, K., Itou, Y., Yanazawa, M., Ohsawa, M., Suzuki-Migishima, R., Umeki, Y., Hohjoh, H., Yanagawa, Y., Shinba, T., Itoh, M. *et al.* (2009) Three human ARX mutations cause the lissencephaly-like and mental retardation with epilepsy-like pleiotropic phenotypes in mice. *Hum Mol Genet,* 18, 3708-24.
- Lee K., Mattiske T., Kitamura K., Gecz J., Shoubridge C. (2014) Reduced polyalanine-expanded Arx mutant protein in developing mouse subpallium alters Lmo1 transcriptional regulation. *Hum Mol Genet,* 23, 1084-94.
- Shoubridge C., Fullston T., Gecz J. ARX spectrum disorders; making inroads in to the molecular pathology (2010). *Hum Mut* 31, 889-900.
- Shoubridge et al. (2010) Mutations in the guanine nucleotide exchange factor gene IQSEC2 cause nonsyndromic intellectual disability. Nat Genet 42(6):486-488.
- Shoubridge C., Tan M.H., Seiboth G., Gecz J. Missense mutations in the homeodomain of ARX abolish binding to DNA and cause a loss of transcriptional repression activity. (2012) *Hum Mol Genet*, 21, 639-47.

Paediatrics and Child Health, Flinders Medical Centre

Supervisor/Contact Persons

Dr Dani-Louise Dixon
Phone: 8204 5494
dani.dixon@flinders.edu.au

Prof Kevin Forsyth
Phone: 8204 5259
kevin.forsyth@flinders.edu.au

Major Interests

- Child Health
- Strategic planning in health care delivery for children
- Paediatric Immunology and Paediatric Infectious Diseases
- Research in the immunopathology of inflammation, particularly viral induced respiratory disease in infants
- Immunisation
- Medical Education
- Curriculum reform in the teaching of Child Health at both undergraduate and postgraduate levels
- Use of Information Technology in teaching and learning

PROJECT: Decreasing neutrophil-induced lung damage in respiratory syncytial virus (RSV) infection: a means to ameliorate infant bronchiolitis.

Project Background

Bronchiolitis is the most common severe respiratory tract illness in infants and remains a major cause of infant hospitalisation as currently there is no treatment. Strong evidence suggests that the virus which causes bronchiolitis, RSV, induces host immune cells (neutrophils) to damage the lung, increasing disease severity as well as leading to the development of asthma in up to 50% of patients.

Recently our lab demonstrated the ability of a protein, feG, to prevent and treat such lung damage.

We aim to test the therapeutic potential of feG in decreasing lung damage caused by RSV, utilising a range of techniques which may include in vitro (cell culture), animal models, and/or clinical (human) aspects.

The project will be conducted in the Lung Injury Laboratory within the discipline of Critical Care Medicine. The lab has expertise in fields as diverse as immunology, pathology, anatomy, histology, physiology, and molecular biology and undertakes research that crosses all of these disciplines, in both laboratory based and clinical projects. The Laboratory has an excellent international reputation and an outstanding record of obtaining funding from government and non-government sources resulting in regular publication in top international journals.

Translational Research Unit, Genetics and Molecular Pathology, SA Pathology

Supervisor/Contact Person

Dr Maria Fuller
Phone: (08) 8161 6741
maria.fuller@adelaide.edu.au

Location: Women's and Children's Hospital

The Translational Unit is embedded in the larger Genetics and Molecular Pathology Directorate in the state-wide pathology service, SA Pathology, and collaborates with a number of other research groups, locally, interstate and overseas. The Directorate provides a diagnostic service for patients with inborn errors of metabolism, not only within South Australia, but nationally and internationally. Inborn errors of metabolism are relatively rare genetic disorders caused by an inherited deficiency of an enzyme or its cofactor and have a devastating impact on the child and family. Consequently, the metabolite for this enzyme and/or cofactor cannot be metabolised and accumulates in affected cells resulting in progressive and debilitating disease. Our primary research interest focuses on inborn errors that manifest with a neurodegenerative phenotype and is aimed at interrogating lipid metabolism using a high throughput mass spectrometry 'lipidomics' platform for the analyses of patient samples as well as cell and mouse models for these neurodegenerative disorders. The outcome of the Translational Unit is 1) to develop and then translate new testing parameters into the diagnostic service to improve the efficiency and accuracy of diagnosis for inborn errors of metabolism, 2) use lipids to biochemically track patients to monitor disease progression and therapeutic intervention, and 3) to understand the disease process in order to identify new therapeutic targets that could be developed for clinical use.

Students can join ongoing projects in the following areas all using the latest mass spectrometry technology. Students will gain an insight into the biology of brain disease, genetic diseases and learn a large number of laboratory techniques and methods including state-of-the-art mass spectrometry technologies. Students will also have the opportunity to combine scientific research with diagnostic testing and interactions with a specialised service laboratory.

Project 1: Multiplex analyses for progressive genetic brain diseases

Supervisor: Maria Fuller and Nicholas Smith

Project Background

Inherited neurodegenerative disorders present throughout life, although disease burden is greatest in childhood. The diseases result in progressive loss of neurocognitive function and in the most aggressive forms inevitable declination to a dependent vegetative state and premature death.

Current diagnostic pathways remain inadequate, with many patients not receiving a correct diagnosis and for others the diagnosis is often delayed - an extremely stressful process for the child and family. There are no cures, and as yet no effective treatments, with therapeutic intervention limited to a small subset of cases. While definitive pathogenic mechanisms of disease remain poorly understood, disordered brain lipid metabolism has been strongly implicated. This project proposes a "lipidomics" approach to identify possible lipid biomarkers that could be developed into a mass spectrometry-based laboratory test for the diagnosis of neurodegenerative disorders using plasma and central spinal fluid samples that we have from referrals to our diagnostic service. This provides a unique opportunity to develop disease specific signatures through lipidomic profiling amongst the spectrum of inherited neurodegenerative illnesses. Additionally, the identification of lipid abnormalities may lead to the identification of novel treatment targets exploring the possibility of interfering with lipid metabolism as a therapeutic strategy for these diseases.

Students have the opportunity to interrogate lipid alterations in particular subsets of neurodegenerative diseases.

References

- Meikle PJ, Whitfield PD, Rozaklis T, Blacklock D, Duplock S, Elstein D, Zimran A, Mengel E, Cannell P, Hopwood JJ, Fuller M. (2008) Plasma lipids are altered in Gaucher disease: Biochemical markers to evaluate therapeutic intervention. *Blood Cells Mol Dis* **40,** 420-7.

- Cermenati G, Mitro N, Audano M, Melcangi RC, Crestani M, De Fabiani E, Caruso D. (2015) Lipids in the nervous system: from biochemistry and molecular pathology to patho-physiology. *Biochim Biophys Acta* **1851,** 51-60.

Project 2: The neuronal lipidome: a therapeutic target for neurodegenerative disorders

Supervisors: Maria Fuller and Nicholas Smith

Project Background

Neurons, specialised cells that form the basis of data processing within the brain, contain extensive amounts of surface membranes due to their elaborate labyrinth of axons and dendritic spines. Lipids are the major constituents of these membranes and although abnormal accumulation of lipids in inborn errors of metabolism is increasingly recognised, virtually nothing is known about their pathophysiology. It is conceivable that if the finer, structural detail of these lipid abnormalities could be realised, then their correction may present a therapeutic strategy.

As structural cells, gilal cells and astrocytes, comprise the majority of the brain, primary neuronal cultures will be isolated and cultured. Temporal alterations in neuronal lipid composition will be defined through interrogation of cultures at day 7 (immature neurons) and day 21 (mature neurons). Furthermore, location of the lipids within the neuronal membranes will be determined by isolating membrane microdomains and determining the individual lipid composition of highly specialised membrane regions involved in signal transduction. This project will suit a student who is keen to develop a strong skill in cell culture, in addition to cell biology and lipidomics.

References

- Hein LK, Duplock S, Hopwood JJ, Fuller M. (2008) Lipid composition of microdomains is altered in a cell model of Gaucher disease. *J Lipid Res* **49,** 1725-1734.
- Dawson G. (2015) Measuring brain lipids. *Biochim Biophys Acta* **1851,** 1026-1039.
- Aureli M, Grassi S, Prioni S, Sonnino S, Prinetti A. (2015) Lipid membrane domains in the brain. *Biochim Biophys Acta* **1851,** 1006-1016.

Project 3: Fatty acid supplementation to alleviate neuropathology for inborn errors of metabolism

Supervisors: Maria Fuller and Ainslie Derrick-Roberts

Project Background

Brain disease remains an unmet clinical need for patients with inborn errors of metabolism. The membranes of mammalian cells are composed of an ordered array of lipids, and in many instances chemical or functional changes in these membranes are central to the pathogenesis of disease. We have shown that membrane lipids are altered and furthermore can be corrected by interfering with the structure of the lipids by regulating dietary fatty acids. This project proposes to measure a range of lipids using high throughput mass spectrometry technology and then attempt to correct them with fatty acids.

Students have the choice of using cell models of disease and performing *in vitro* studies by supplementing the culture media with fatty acids and then assessing the effectiveness biochemically by measuring the lipids afterwards. Alternatively students may use mice models of disease by feeding special chow that is supplemented with fatty acids to the mice coupled with behavioural testing to assess the outcomes on memory and learning.

References

- Hein LK, Duplock S. and Fuller M. (2013) Selective reduction of bis(monoacylglycero)phosphate ameliorates the storage burden in a THP-1 macrophage model of Gaucher disease. *J Lipid Res* **54,** 1691-1697.
- Bigford GE, Del Rossi G. (2014) Supplemental substances derived from foods as adjunctive therapeutic agents for treatment of neurodegenerative diseases and disorders. *Adv Nutr* **5,**394-403.

Vaccine Safety Research Group

Supervisor/Contact Person

Dr Mike Gold
Phone: 8161 7266
michael.gold@adelaide.edu.au

Location: Women's and Children's Hospital

Despite the public health benefit of vaccination, concern about the safety of vaccines may be the most important issue to affect immunisation coverage and the sustainability of an immunisation program. There is a limited capacity to evaluate all aspects of vaccine safety before vaccines are approved for use. This is because the safety evaluation of new vaccines takes place during clinical trials, which usually include thousands of healthy subjects (which is an adequate number for the purposes of detecting common adverse events), and involves a short period of post-vaccination monitoring. Unfortunately, this process does not identify adverse events which are rare, delayed, occur with specific vaccine combinations or in a sub-group of children with co-existing disorders.

Passive surveillance of adverse events following immunisation (AEFI) is used as the primary mechanism for safety surveillance following vaccine licensure; however, this also has limitations which include underreporting and the inability to establish a casual relationship between immunisation and a specific adverse event. In Australia, other mechanisms of surveillance are currently in use; known as enhanced passive surveillance and active sentinel surveillance. Given the limitation of resources, it is important to determine the most effective mechanism of surveillance for an AEFI.

The vaccine safety research group is a multi-disciplinary group, funded by the Australian Research Council (ARC) to investigate the role of data linkage to assess vaccine safety in Australia. The project involves an investigation of the technical feasibility and privacy issues required for data linkage. One of the aims of the project will be to compare the effectiveness of surveillance, using data linkage, with other methods of surveillance currently being used in Australia. This honours project will assess the performance of three methods of surveillance for three sentinel conditions which may occur after immunisation.

PROJECT: A comparative analysis of the surveillance of intussusceptions, seizures and anaphylaxis following immunisation in Australia – 2007 to 2009.

Project Background

Intussusception, seizures, and anaphylaxis are all important adverse events for surveillance following immunisation. In Australia, health providers are asked to report these events to the Adverse Drug Reactions Committee (ADRAC) of the Therapeutic Goods Administration (TGA). However, these events have also been under surveillance using enhanced passive surveillance and active sentinel surveillance. The Australian Paediatric Surveillance Unit (APSU) conducts enhanced passive surveillance by requesting monthly AEFI reports from paediatricians. Active sentinel surveillance is conducted through a Commonwealth initiative known as Paediatric Enhanced Disease Surveillance (PAEDS). This scheme funds part-time specialist nurses in four tertiary care hospitals in Australia (SA, NSW, Vic, and WA) to identify children with an AEFI. Detailed clinical data and biological samples are collected and additional information on risk factor and vaccination history is sought from parents. The aim of the project will be to evaluate the effectiveness of these three surveillance methods by comparing data, which has already been collected. The skills required will be an interest in one or more of the following areas: public health, pharmacovigilance, paediatrics or immunisation. The techniques will involve analysis of AEFI reports and comparative data analysis. The student will be supported by the group who have skills in statistical analysis of data, and vaccine safety.

References

- JML Brotherton, MS Gold, AS Kemp, PB McIntyre, MA Burgess, S Campbell-Lloyd, on behalf of the New South Wales Health HPV Adverse Events Panel CMAJ. 2008 Sep 9;179(6):525-33.
- Monitoring vaccine safety: a critical component of every immunization programme Brotherton J Gold M. Med J Australia 2008: 189(5):243-244
- Human papillomavirus vaccine hypersensitivity reactions – a retrospective cohort study in Australia. Liew WK, Nigel Crawford N, Tang M, Buttery J, Royle J, Gold M, Zeigler C, Quinn P, Elia S, Choo S. BMJ 2008: 337;a2642
- Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies. Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS et al ; The Brighton Collaboration Methods Working Group. Vaccine. 2009 Apr 6;27(16):2282-2288.
- Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS, et al The Brighton Collaboration Methods Working Group. Vaccine. 2009 Apr 6;27(16):2289-22

Vaccinology and Immunology Research Trials Unit

Associate Professor Helen Marshall

Dr Sue Evans
Dr Trinh Tran
Dr Suja Mathew

Mrs Christine Heath
Mrs Michelle Clarke
Mrs Kirsten Zyhajlo
Mrs Mary Walker

Mrs Verity Hill
Ms Susan Lee
Mrs Jane Tidswell
Ms Bing Wang
Ms Joanne Collins

Location: Women's and Children's Hospital

Supervisor/Contact Person
Associate Professor Helen Marshall
8161 8115
helen.marshall@adelaide.edu.au

The Vaccinology and Immunology Research Trials Unit, is a multidisciplinary immunisation research group at the Women's and Children's Hospital, affiliated with the University of Adelaide and part of the Children's Research Centre, University of Adelaide. The centre's membership includes internationally renowned experts in paediatrics, immunology and public health. VIRTU's research program includes clinical trials in investigational vaccines, infectious disease epidemiology, social epidemiology, immunology and public health.

Current research programs include:

1. Investigational vaccines; meningococcal B vaccine, (pre) pandemic flu vaccines, influenza vaccine, pertussis immunisation at birth, Respiratory Syncytial Virus (RSV) and Parainfluenza Virus vaccine (PIV3)
2. Infectious disease epidemiology; severity of pertussis (whooping cough) infection in hospitalised children, RSV epidemiology and severity of disease in hospitalised children, rotavirus vaccine effectiveness
3. Immunisation of children at special risk; Human Papillomavirus vaccine
4. Social epidemiology; Pandemic influenza community preparedness, HPV school immunisation program; why are girls opting out?, and enhanced surveillance of paediatric conditions of public health importance

Clinical/Public Health Relevance

Conducting trials in investigational vaccines provides local Australian data for licensing authorities. Studies of investigational vaccines conducted at our centre provide Australian data for regulatory authorities such as the Therapeutic Goods Administration (TGA) and Food and Drug Administration, (FDA, US). It is an advantage for both vaccine companies and the TGA to have safety and immunogenicity data based on the Australian population when licensing of a new vaccine is being considered. Other significant contributions include studies in new combination vaccines. This allows a reduction in the number of needles that need to be administered to infants and children making vaccination more acceptable (and more cost-effective with less time spent in the clinic) for all involved. Many of the new vaccine combinations trialled by our unit are now licensed (or have been filed for licensing) for use in Australian children including a combination measles, mumps, rubella, varicella vaccine. Studies in vaccine safety identify adverse reactions associated with vaccination and provide data that support changes to the vaccination schedule to reduce the adverse effects associated with immunisation. Studies in epidemiology of

disease provide data used to determine whether development of a vaccine to prevent an infection is feasible and guides the scheduling of the vaccine in the National Immunisation Program. Our group also conducts research into community attitudes and acceptance of new vaccines to encourage engagement of the community in immunisation policy decisions. All studies have resulted in a publication or recent preparation of a manuscript for publication.

PROJECT: Influenza infections in South Australia; identifying risk factors of severe disease and complications from influenza in children and adults to inform influenza immunisation policy.

Project Background

Influenza infection can result in an illness that ranges from mild symptoms such as headaches, fever and cough, to life threatening illness with complications including pneumonia and seizures. National and state data suggest that young children (aged <5) and the elderly (>65 years) are at the highest risk of illness due to influenza infection. Vaccination strategies to prevent influenza are currently targeted at the elderly and other individuals with risk factors including medical conditions such as asthma and heart disease, but vaccination of healthy children, whilst recommended, is not currently funded. Understanding the population most at risk of influenza illness, and particularly severe influenza requiring hospitalisation is essential for informing public health policy and guiding vaccine recommendations. This project aims to review state-wide notifications for influenza reported in 2013 and will provide epidemiological data to describe the population affected. Vaccination history and hospitalisation status will also be reviewed for notifications for influenza infections in children aged <5 years old with notified influenza to provide valuable information regarding risk factors for more severe disease and the current prevention strategies.

PROJECT: Parental acceptance of influenza vaccination for children under five years of age

Project Background

Influenza infection causes significant disease in Australia. Almost 45,000 cases of influenza occur in Australia annually, with approximately 30% of cases occurring in children. Influenza notification and hospitalisation rates are highest in young children where transmission occurs rapidly. Despite influenza infection causing substantial disease and a vaccine being licensed and recommended for children over 6 months of age, influenza vaccination is not part of the National Immunisation Program which is funded to provide all Australian children with routine scheduled immunisations (such as whooping cough, measles and chicken pox vaccinations). Influenza vaccination is provided free for children with specific risk factors for influenza such as chronic disease or impaired immunity. Influenza coverage data for children is unclear but historically low (<10%) and it is unclear whether this is due to a lack of perceived value, or other barriers such as cost or access.

The Aims of this study are to improve our understanding about barriers for vaccination of young children in South Australia. We will engage the community, in particular Parents of young children, to determine what value they place on influenza vaccination and to collect information regarding the reasons they have for either choosing to, or not to vaccinate their children against influenza. We will also collect data on current season or prior season influenza vaccinations for randomly selected participating households to determine uptake rates in South Australian populations.

PROJECT: The role of midwives in promoting maternal immunisation

Project Background:

Immunisation during pregnancy provides dual benefit to both mothers and newborn infants. It is the most viable option to prevent infectious disease and poor outcomes, in particular for infants, who are too young to be protected by current immunisation schedules, as they are most likely to experience serious complications or death. Despite medical recommendations for women to immunise during pregnancy, vaccine uptake is suboptimal. Healthcare providers involved in antenatal care are critical to recommending and maximising vaccine uptake to women during pregnancy. Midwives play a crucial role in providing antenatal care to pregnant women, even greater in midwifery-led care models where pregnant women may not be cared for or seen by an obstetrician during their pregnancy. Although midwives are key healthcare providers in the antenatal setting, there is a lack of research on their specific role in facilitating maternal immunisations. Although previous studies have identified antenatal advice from health care providers as an important factor that promotes immunisation, no large-scale studies have occurred to date that specifically focus on the perspectives and practices of midwives within the antenatal setting.

This study seeks to examine midwives' attitudes towards the use of vaccines during pregnancy and whether they recommend immunisation to pregnant women. The aim is to explore and identify attitudes, barriers, facilitators towards maternal immunisation.

There are potentially **two projects** available within this topic, one will use a quantitative methodology using a questionnaire and the other will use a qualitative approach using semi structured, one-to-one interviews with a number of midwives from the two hospitals. Both studies will evaluate key differences in knowledge and attitudes of midwives who support

maternal immunisations and recommend in practice and those who do not or are hesitant. The qualitative study will also seek to develop optimal strategies for midwives to recommend maternal immunisations and together with midwives design an intervention to increase vaccine uptake. It will provide new evidence to inform an appropriate midwife-led intervention on the key messages midwives need to successfully promote to pregnant women and incorporate in practice.

1. To describe, and explore factors that are motivators and barriers to midwives recommending maternal immunisations to pregnant women.

2. To investigate and determine the reasons for recommending or not recommending maternal immunisations in practice.

3. To explore strategies that increase midwives' knowledge and confidence in recommending maternal immunisation.

4. To develop an initiative with midwives to improve uptake of vaccines for pregnant women

PROJECT: Validity of parent-reported medical conditions in children with high risk medical conditions

Project Background

A child's parent-reported medical history is, in general, assumed to be accurate. Precise ascertainment of the presence of disease is critical for clinical and research purposes. Diagnoses are commonly used for risk adjustment in epidemiological studies. Research efforts using survey data are often predicated on a presumed accurate history from parents of their child's past and current medical problems. The likely validity of self-report of a person's medical conditions helps guide researchers to expend resources and attention to adjudicating those diseases in which self-report is likely to have lower validity. No studies have evaluated the agreement between parent-report and medical records in children with high risk medical conditions.

This study, using survey and medical records data, aims to investigate the accuracy of using medical conditions captured through survey data by: (1) measuring the agreement between self-reported medical conditions and recorded medical diagnoses and (2) identifying patient characteristics and conditions that predict higher or lower levels of agreement in a cohort of children with high risk medical conditions at the Women's and Children's Hospital.

PROJECT: Motivations and experiences of participating in paediatric clinical research

Project Background

Clinical trials are research investigations that use human subjects to contribute to knowledge that can be applied to benefit society. These studies are indispensable for the progress of medicine in general. In vaccinology, they are particularly useful for measuring ongoing protection and scheduling etc. However, the use of human subjects in these studies as a unit of analysis introduces certain challenges and some studies can require subjects to continue participation in a research protocol over many years. However, little is known about the factors that influence willingness to participate in vaccine trials, particularly for children. Designing strategies that enhance vaccine trial recruitment and retention are critical and developing informed consent processes and standards of care have ethical implications.

This study will use qualitative and quantitative research methodologies to explore the motivators, social-demographic profile and experiences of participating in clinical trials in the VIRTU, located in a major paediatric hospital.

There are potentially **two projects** available within this topic, one will use a quantitative approach using a questionnaire and the other will use a qualitative approach using semi structured one-to-one interviews with a number of previous participants from clinical trials.

Wound Healing Laboratory, Regenerative Medicine

Principal supervisor:
Dr Zlatko Kopecki (Mawson Lakes Campus)

Co-supervisors:
Prof Allison Cowin (Mawson Lakes Campus)
Prof Gordon Howard (Adelaide University, Roseworthy Campus)
Location: Mawson Institute

Contact Persons
Dr Zlatko Kopecki
83026384
zlatko.kopecki@unisa.edu.au

Group Research Focus
Our laboratory comprises a large team of dedicated scientists working to understand the intricate mechanism of wound healing and develop novel therapy for treatment of different types of wounds, including skin wounds and injured mucosal tissue following inflammation or blistering. Using different animal models of human disease, we have developed an antibody therapy which when applied locally improves the rate of skin healing and decreases scarring. Our current laboratory research interest focus includes investigating the best possible antibody delivery options for treatment of injured mucosal tissue systemically. One of those delivery options would be investigated in this Honours project

PROJECT: Systemic delivery of an antibody for the treatment of injured mucosal tissue

Aim of project: To investigate if systemic FnAb administration reduces the extent of mucosal inflammation and blistering following chemically induced model of inflammatory bowel disease.

Project Background

Our laboratory has identified an important cytoskeletal protein called Flightless (Flii), which is important during development but also increases during tissue inflammation and injury. Flii mediates tissue inflammation and regulates cellular responses during tissue repair. We have developed Flii neutralising antibodies (FnAb) which when applied to skin wounds locally improve the rate of healing and decrease the extent of tissue scarring. Our preliminary data shows that Flii also plays a role in mediating inflammatory tissue damage in inflammatory bowel disease. High Flii levels contribute to increased mucosal tissue damage and disease severity suggesting that lowering Flii levels using FnAb is an attractive approach treatment for inflammatory bowel conditions as primary or secondary disease manifestations. Systemic antibody treatments are becoming increasingly popular in both human and veterinary medicine for a range of conditions. In this project we would investigate the effect of systemic targeted FnAb delivery to the gut using a well-developed model of inflammatory bowel disease in our laboratory. In addition, the student will perform in-vitro biochemical assays using epithelial colon cells to determine the effect of FnAb on tissue inflammation and cell function. These studies will be the first to demonstrate the effect of systemic FnAb antibody delivery on mucosal inflammation in a chemically induced model of inflammatory bowel disease in-vivo and may pave a way for human clinical trials using systemic delivery of FnAb.

Methodology to be used: This project will involve use of well-established DSS induced model of bowel disease in mice, collection of blood and disease and normal tissue controls, histological processing of samples, protein biology (immunohistochemistry and western blotting), biochemical analysis of tissue and blood samples (MPO assay, WST-1 assay, ELISA), light microscopy, epifluorescence and confocal fluorescence microscopy

Other information: You will be a part of a large multidisciplinary research team which consists of Post-doctoral researchers, research assistants and both PhD and Honours students working in the friendly team environment. You will be directly trained, supervised and supported to ensure timely and efficient completion of your studies. The institute and your supervisors will be able to support your work financially and resource-wise.

Possible scholarship applications: Zonta Club of Adelaide Honours Scholarship

Expected Outcomes: Our laboratory has a proven track record (with high number of both Honours and PhD students (past and present) in providing students all support necessary and designing successful projects for students to complete their studies with first class Honours and top PhD results as well as good publication record. These studies will provide you with the necessary knowledge or experience to enter the workforce or continue to pursue PhD research. Expected outcomes from the research study include – improved healing of damaged/injured mucosal surfaces with optimised delivery system which may lead to human clinical trials and help a large number of Australians suffering from inflammatory bowel disease or skin blistering conditions where mucosal surfaces are also compromised.

Index

Discipline of Obstetrics and Gynaecology
Discipline of Paediatrics
The University of Adelaide
Telephone + 61 8 8313 5100
Facsimile + 61 8313 4099
Email: sprh.l_and_t@adelaide.edu.au
Web: https://health.adelaide.edu.au/paediatrics-reproductive/