



THE UNIVERSITY
of ADELAIDE



Annual Report 2012

Robinson Institute

seek LIGHT



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Vision

By 2020 the Robinson Institute will be a world leader in research for reproductive and paediatric health.

Our discoveries will transform clinical care and policy for the health of all children and families, across generations and global communities.

Mission

To conduct world leading research that generates major advances in human reproduction, pregnancy, child and adolescent health.

Working collaboratively through common themes and focusing on global research challenges, our discoveries will be translated into health practice and social policy for the wellbeing of families across generations.

Our reputation will attract the best international investigators in health and medical research, translation and commercialisation, and we will offer state of the art facilities, training and infrastructure to support research excellence.

Message from the Deputy Vice-Chancellor Research

Outstanding research universities provide society with the fruits of their endeavours and bring about improvements in people's lives. At the University of Adelaide we have established five research institutes which have been tasked with addressing 'grand challenges' affecting our communities now and into the future. One of these challenges is securing a healthier future for our children.

The Robinson Institute aims to uncover the factors that influence health across our lifetime and between generations. With over 450 members, the Institute is making significant improvements in reproductive and paediatric health. In 2012 alone researchers established new guidelines around induction of labour to save babies lives; showed for the first time that the brains of adolescents born preterm (even if only by a week or two) may suffer learning and memory difficulties; and proved that overweight and obese fathers can not only impair pregnancy outcomes, but also the adult health of the next generation.

As you read through the stories within this Report, you will appreciate the great breadth and depth of the research being undertaken at the Robinson Institute. I would personally like to commend members of the Institute for the enormous amount of work they have invested throughout 2012 in re-shaping the organisation. This has delivered a clearer vision and structure to help catalyse greater collaboration among its members.

With this strong future direction and excellent track record, the University decided to award the Institute a second 5-year term to commence in August 2013. I expect that, over this time, we will see the Robinson Institute continue to bring to light new discoveries, transforming clinical care and policy for the health of all children and families, across generations and global communities.

Professor Mike Brooks
Deputy Vice-Chancellor and Vice-President Research



Chairman's report



The year 2012 was a transformational year for the Robinson Institute, in a number of respects.

Culture change has been the fundamental principle underpinning and guiding the development of the Robinson Institute since its founding – moving to cross-Institute collaboration, thinking and funding, whilst enhancing excellence of existing approaches.

'Reshaping the Robinson' has become a program of integrated developmental change within the Institute, under the guidance of a Transition Management Committee. We are moving to an integrated Institute with a focus on Research Themes and Challenges and shifting away from funding Centres. Significant work has been done in further developing relationships with key external stakeholder organisations, and in streamlining the administrative arrangements between the Institute and the School of Paediatrics and Reproductive Health.

Now in their 5th year, I believe the governance arrangements for the Robinson have well-served the Institute and the University of Adelaide. Board membership has included those in senior roles within the University, and from outside the University and interstate. These individuals have brought diverse, positive and very helpful perspectives and inputs.

Those around the Robinson Board table – including Director Rob Norman and General Manager Kate Irving – have brought well-considered and insightful contributions, worked in a collaborative way, and sought to collectively 'find a way' through multi-stakeholder and often complex and sometimes contentious issues.

During the year we farewelled Professor Tanya Monro, Professor Bik To, Professor Jonathon Morris, Ms Mary Patetsos and Mr Phil Robinson. I thank each of them for their contributions to the work of the Board, and the Robinson generally. We welcomed Professor Julie Owens (Head of the School of Paediatrics and Reproductive Health) and Ms Gail Mondy (Chief Executive Officer of the Women's and Children's Hospital) to the Board, and we look forward to their input.

The ongoing Board members – Professor Mike Brooks, Professor Justin Beilby, Professor Jock Findlay, Professor Marie Dziadek, and Professor Paul Rolan – have been with the Robinson Board from the outset. To each of them I acknowledge their commitment, considered guidance and general 'value-add', and thank them for this.

As a result of the positive conclusion to the external review of the Robinson undertaken during the previous year, the University of Adelaide made clear its ongoing support

“ 'Reshaping the Robinson' has become a program of integrated developmental change within the Institute ”

for the Robinson, agreeing to a second 5-year funding cycle, with increased levels of financial support. We are grateful for this – it has provided a firm foundation upon which to move to take the next important steps in 2013 toward developing the Institute as an Advanced Health Science Centre, including the critical element of securing a successor as Director to founding Director, Professor Rob Norman.

The University has in turn been rewarded for its support with outstanding results in the Excellence in Research (ERA) Initiative. In the research field of paediatrics and reproductive health, it was awarded the top rating of 5 – well above world standard – the only University in Australia to do so in both 2012 and 2010.

In light of the above, I am confident in the Robinson's future, although not complacent – more remains to be done to embed past innovations, and to respond to ongoing dynamic environment in which the Robinson operates.

My thanks to Kate Irving, General Manager, and her team for great work during the year.

Finally, I pay tribute to Professor Rob Norman, founding Director of the Robinson Institute, acknowledge his wonderful leadership of the Institute, and thank him for his contribution, without which the Robinson would not have been launched, let alone be at its current stage, poised for a successful future. 2013 will see Rob stepping down from the Director role, and also mark his 25 years with the University of Adelaide.

Mark Coleman
Chairman

Director's report

Our vision for the Robinson Institute started in 2006 when Professor Julie Owens, Mr Michael Guerin and I saw the opportunity to bring disparate groups together with a common purpose to improve the quality of research in reproduction, paediatrics and stem cell biology, with the aim of improving health for all Australians.

It took nearly two and a half years before the Robinson Institute started and we soon came to the realisation that the Institute could not be a 'banker' that simply handed out money, but rather an 'investor' seeking to maximise gain for all members involved in research in these areas. 2012 was the year when it all came together for the Institute. We moved to de-emphasise the role of Centres in an effort to maximise collaboration. A series of meetings and workshops were held, which ultimately transitioned into the development of Research Themes and Research Challenges. This has made it much easier for us to focus on real health outcomes and to encourage researchers to work together and not compete against each other. We now have four major Research Themes and 10 Research Challenges; we consider our researchers work in communities and to support them we have to develop Core Facilities. The movement to a Theme based operating model is seeing an environment of cross collaboration emerge and these will replace the original centre based model. We need to support the Communities, Themes and Challenges and a key element of this is the investment in developing Core Facilities.

2012 was also the year in which, for the second time, our efforts were rewarded by the Australian government's Excellence in Research Australia (ERA) score of 5 in paediatrics and reproductive health – and again the only group in Australia to receive that score. While we will no doubt be joined by others in the country in the next round, the quality and volume of work coming from our researchers indicates that we are one of the leading centres in the world in our area of research.

“...we are one of the leading centres in the world in our area of research”



There were many achievements in this year but I would like to highlight two in particular that show our contribution to real health outcomes. The first is a publication by Professor Michael Davies and colleagues in the New England Journal of Medicine in which they linked various databases to investigate outcomes for children from IVF procedures. Reproductive technology is one of our strongest areas and this paper indicated that while there is some cause for reassurance about the outcome of IVF children, there is no room for complacency. This paper received the highest publicity of any output from The University of Adelaide last year. The second is the enormous study conducted by Professor Jodie Dodd at the Women's and Children's Hospital, in which she randomised more than 2,000 women who were overweight in pregnancy to a lifestyle intervention or to standard care. The remarkable achievement in getting full recruitment, coupled with the usual detailed planning and analysis will make this study ground-breaking and will lead to many more papers over the next few years.

Members of the Institute made major contributions to community engagement including the highly successful Healthy Development Adelaide which continues to engage with researchers, government and the community on matters to do with paediatrics and reproductive health. Emeritus Professor Alastair MacLennan co-founded the Friends of Science which seeks to put objectivity back into the analysis of many claims in popular culture regarding the efficacy of

unproven substances and practices. Members of the Institute were frequently cited in electronic and print media for their discoveries. In addition, we played prominent roles in the National Health and Medical Research Council, Australian Research Council and professional societies including the Society for Reproductive Biology, Perinatal Society of Australia and New Zealand, Fertility Society of Australia, Asia Pacific Initiative on Reproduction and many others.

October 2013 marks my stepping down from Directorship of the Robinson Institute at a time when we have established good governance, trust with the University administration, benefit for our members and an active pipeline of discovery from basic science through to health policy and practice. There is much to be proud of in what we have achieved over the last five years but there are many challenges ahead with reducing government funding for research, a leadership transition and developing relationships with the South Australian Health and Medical Research Institute and the Women's and Children's Health Research Alliance. I would like to thank Board Chair, Mr Mark Coleman, and General Manager, Ms Kate Irving along with her staff, for the outstanding support they have given me.

Professor Robert Norman
Director

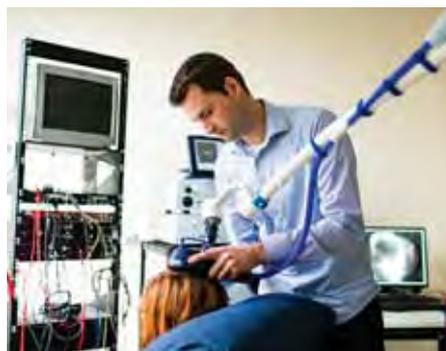
Robinson Institute at a glance



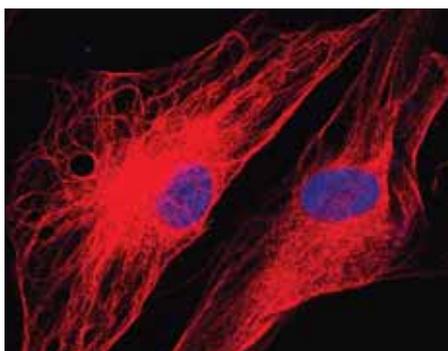
More than
\$23m
in funding in 2012



More than
50 research
leaders and
450 members



5 research centres



10 Research
Challenges



Raised more than
\$150,000
for the Peter Couche
Foundation in 2012



Embedded in
5 SA hospitals



More than
30 Honours
students



More than
110 PhD
students



More than
350 publications
in 2012



Raised more than
\$50,000
for the Robinson
Foundation in 2012



Multiple national
and international
collaborations



5 new patents
filed



About the Robinson Institute

The Robinson Institute brings together more than 450 members in reproductive and paediatric health, who are dedicated to providing all children with the healthiest start in life.

Who we are

The Robinson Institute brings together more than 450 world-leading researchers and clinicians in reproductive and paediatric health, who are dedicated to providing all children with the healthiest start in life.

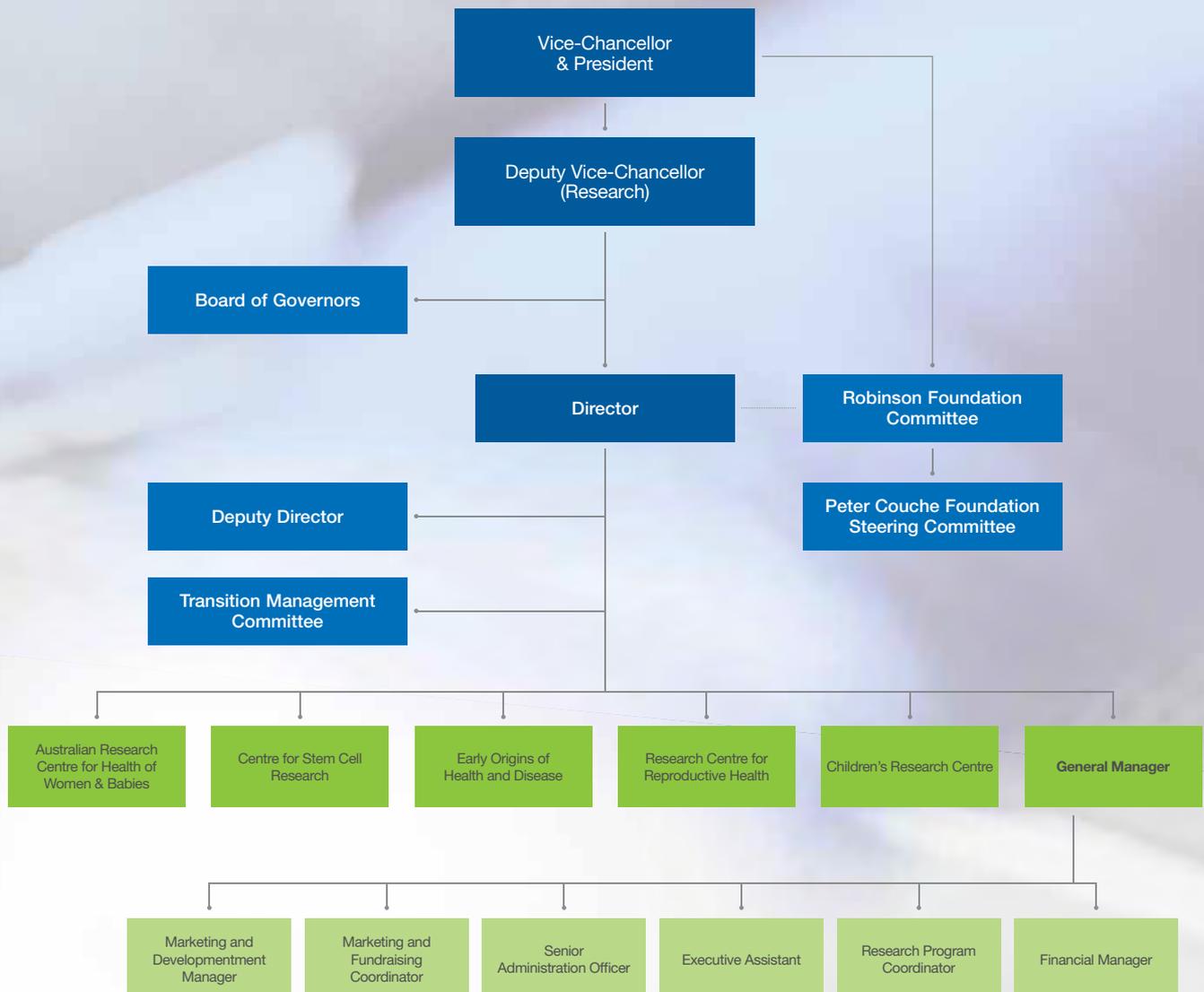
As part of the University of Adelaide, we are internationally renowned for our ground-breaking research and translation into clinical care and health policy.

By focussing on the early stages of life we aim to improve the wellbeing of families across generations. This includes enabling a healthy start through fertility choices and conception, nurturing the unborn during pregnancy, strengthening

the brain and body in early life and advancing child and adolescent health to treat and prevent disease.

To advance our research we are committed to building national and global partnerships which help us address major research challenges. In addition, we seek to engage with the community to build awareness of the value of investing in reproductive and paediatric health, to educate them on the vital nature of our research, and to attract ongoing support. This will ensure our researchers continue to make remarkable discoveries that transform and improve quality of life.

The Robinson Institute: Structure (2012)





A new direction

Throughout 2012, the Robinson Institute underwent a significant transformation to *Reshape the Robinson* operating model for future sustainability.

The reshaping began in November 2011 when an external review recommended that the Institute make a number of key changes to achieve its goal of becoming a world-leading research organisation. This included the development of a bold 10 year vision and a review of the Institute's structure to facilitate greater internal collaboration. Key to this was the recommendation that the Institute transition from a centre based operating model to a research theme based model.

To progress these recommendations the Reshaping the Robinson project was launched, with the first step being to develop Research Themes.

Research Themes

The Research Themes are at the core of Reshaping the Robinson. They provide the necessary infrastructure and focus to operate as a Research theme based organisation - enabling greater flexibility and cross collaboration. To drive theme development the Institute established the 'Theme Development Taskforce'. The Taskforce consulted widely and often with Institute members and staff, driving the initiatives that would help define the themes. This included numerous workshops and open forum consultations, resulting in the establishment of four key Research Themes:

Reproductive Health

Pregnancy Health

Early Origins of Health

Child and Adolescent Health

The Research Themes cover the breadth of the Institute's research and align with the reproductive lifecycle, ensuring that the research improves health and wellbeing across generations.

Research Challenges

Accompanying the development of Themes came the need to identify major Research Challenges. These require diverse expertise and approaches to address significant health burdens nationally and internationally. They will enable the Robinson Institute to demonstrate distinction and achieve research excellence.

Defining the priority Research Challenges upon which to focus and invest, the Institute will clearly demonstrate how its research is aligned to national and global priorities and how it can make a lasting impact. They will also enable researchers from diverse fields and groups to come together, encouraging new ideas and perspectives.

The result of the Research Challenge development process is the Institute's top ten Research Challenges.



Top 10 Research Challenges

1. **Fertility**
Enabling the best start in life

2. **Fetal Growth**
Understanding and optimising growth of the baby

3. **Born Too Soon**
Preventing preterm birth and improving outcomes for babies

4. **Brain Power**
Maximising neuro-developmental potential

5. **Childhood Obesity**
Achieving a healthy weight and metabolism

6. **Reproductive and Childhood Cancers**
Discovering causes and finding cures

7. **Allergy**
Exploring origins of immunity

8. **Mental Health**
Improving the mental health of young people and their families

9. **Protecting Children from Serious Disease**
Preventing and reducing disability in children

10. **Treatment Innovations**
Pioneering interventions to improve the health of children

Core Facilities

As part of the Research Challenge development process, the Scientific Review Panel was asked to make recommendations around how best to invest in our Research Challenges for the next three years to 2015.

During the process it was clear to the Panel that each Research Challenge needed improved facilities, particularly in Bioinformatics, Biostatistics and the management of cohorts and biobanks. Consequently it was recommended that the Institute invest in such facilities to deliver the greatest value.

In response to this recommendation the Robinson Institute has defined its Core Facilities. These are facilities that all researchers need and which the Institute is committed to building, they include:

Bioinformatics
Biostatistics
Intergenerational Studies Management Unit
Gene Silencing and Expression (GSEx) Facility
Research Equipment, Measurement & Assay Facility

2013 will be an exciting year for the Robinson Institute. Reshaping the Robinson will enter implementation phase, requiring the commitment and support of all research leaders, members and staff. This will be a great opportunity for collaboration and input into how the Institute structure can evolve to progress the Research Themes, Research Challenges and establish Core Facilities.

With a clearly defined vision, mission and research priorities there will also be a renewed focus on the work of the Robinson Foundation. The great work of the Institute will be shared with the broader community to demonstrate the importance of ongoing funding for current and future generations.

As a leading research organisation in the field of reproductive and paediatric health, the Robinson Institute will work closely with the South Australian Health and Medical Research Institute (SAHMRI) to define its working relationship. The aim will be to leverage strengths and facilities, so that both parties can contribute fully to the development of research in the state.

For 2013 and beyond another priority will be to recruit new senior members to the Institute and to increase collaborations. This will ensure that the highest standard of research is maintained, and open the doors to new possibilities, in both applied science and basic research. The Institute is fostering an environment that encourages excellence in discovery and translation.

Since its beginnings, more than five years ago, the Robinson Institute has thrived under the leadership of Professor Robert Norman. It has been Rob's passion and innovative approach which has driven much of the Institute's success over this time. In 2013 Rob will step down from his position as Director. This will be an enormous change for the Institute and its members, and Rob and the leadership team will work hard to ensure that the new Director is greeted with a solid foundation upon which to build.

Board of Governors



Mark Coleman
Chair



Prof Marie Dziadek



Prof Jock Findlay



Prof Justin Beilby



Prof Mike Brooks



Prof Rob Norman



Prof Paul Rolan



Mary Patetsos



Prof Bik To



Prof Jonathan
Morris



Prof Tanya Monro



Phil Robinson



Gail Mondy



Prof Julie Owens

Robinson Institute
Management Committee
(Jan – Sep 2012)

Robinson Institute
Transition Management
Committee
(Oct – Dec 2012)



Prof Caroline
Crowther



Prof Michael Davies



Prof Jodie Dodd



Associate Prof
Vicki Clifton



Prof Jenny Couper



Prof Stan Gronthos



Kate Irving



Philippa Middleton



Prof Jodie Dodd



Kate Irving



Prof Rob Norman
Chair



Associate Prof
Mark Nottle



Prof Julie Owens
Chair



Prof Rob Norman
Chair



Prof Julie Owens
Chair



Associate Prof
Mike Ridding



Prof Sarah
Robertson



Prof Ray Rodgers



Prof Sarah
Robertson



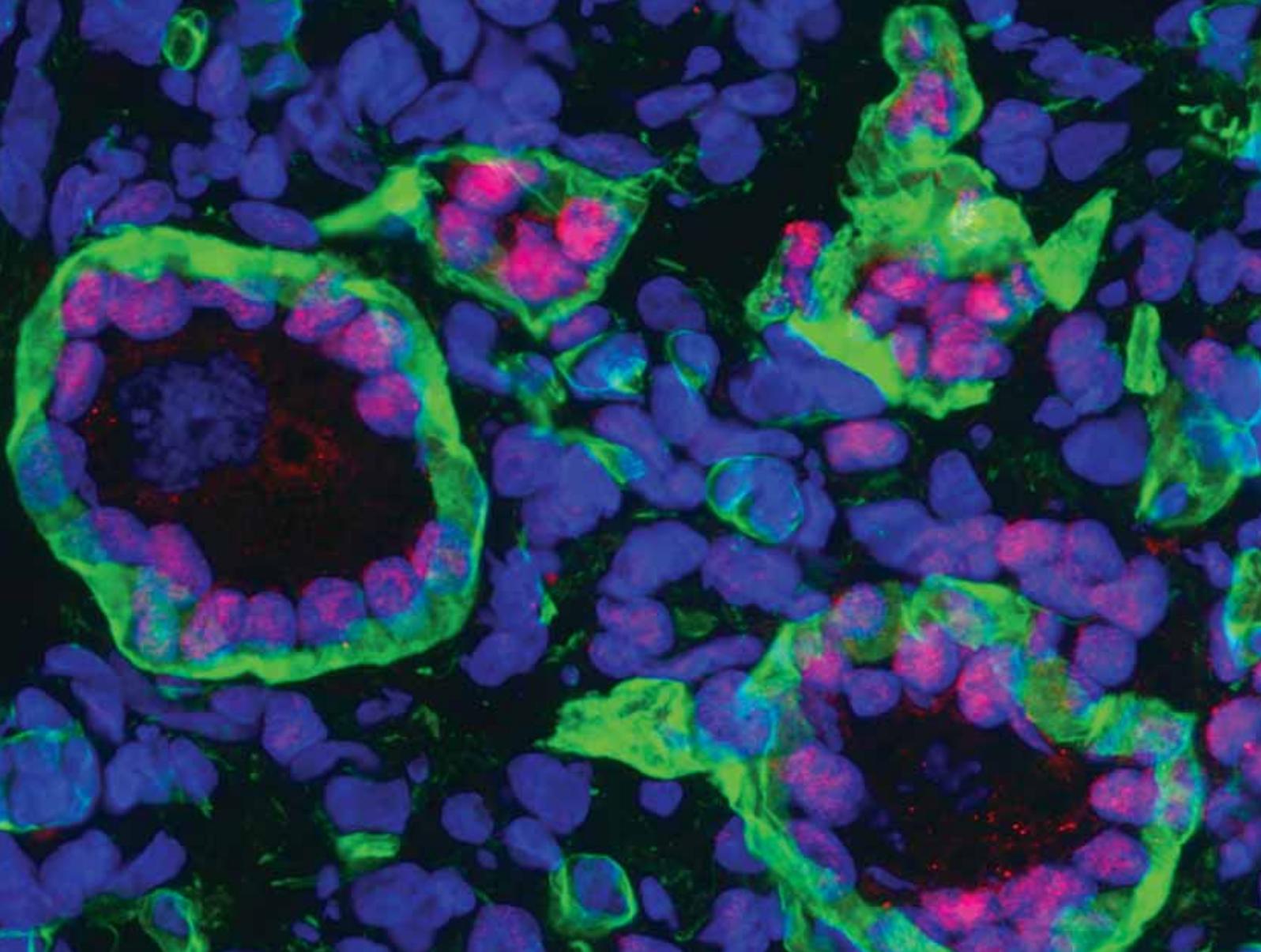
Prof Ray Rodgers



Associate Prof
Darryl Russell



Prof Andrew
Zannettino



2012 Research Highlights

Excellence in Research for Australia

Excellence in Research for Australia (ERA) is an initiative of the Federal Government. ERA is a research quality and evaluation system developed by the Australian Research Council (ARC) in conjunction with the Department of Innovation, Industry, Science and Research (DIISR).

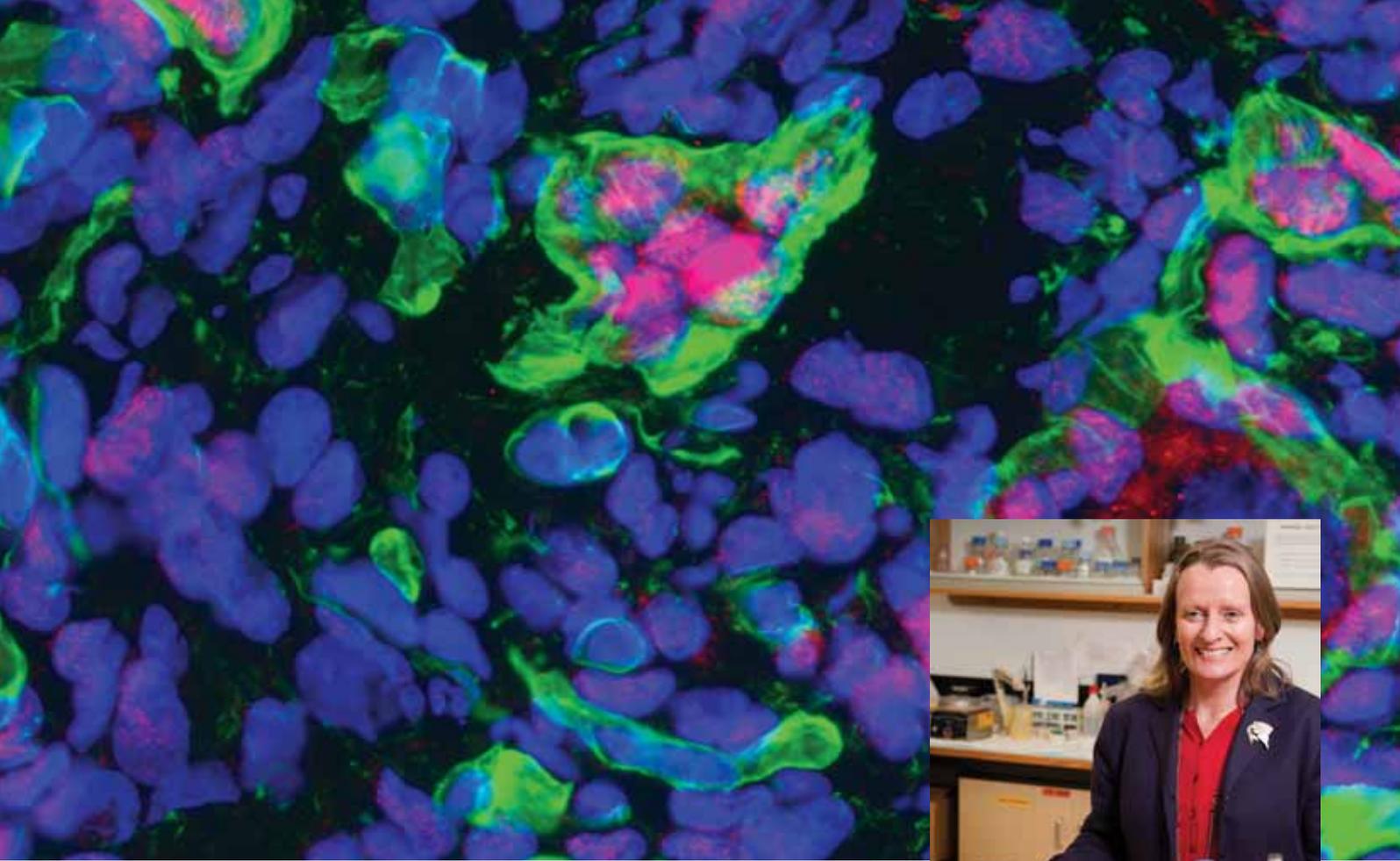
The ERA initiative aims to provide a transparent system to assess research quality, utilising a combination of metrics focused on researchers, research outputs, research income, esteem and applied measures. The information is reviewed at the national level by evaluation committees comprising experienced, internationally-recognised experts.

ERA results were released in 2010 and 2012. The Robinson Institute, through the School of Paediatrics and Reproductive Health, performed at the highest level in both rounds, ranking 5 - well above world standard. This cemented the University of Adelaide's leading position in paediatrics and reproductive medicine - being the only University in Australia to achieve this ranking for the second time running.

Discovery highlights

> Documenting evidence that paternal obesity can induce a sub-fertility phenotype in two generations of offspring in mice. Poor quality sperm and oocytes in the F1 and F2 progeny of males fed a high fat diet were reported by Michelle Lane and colleagues. Importantly, the sperm parameters impaired by obesity are restored by a diet and exercise intervention.

- > Revelation of a new model for how the ovary develops. Ray Rodgers and his group have mapped cell fate decisions in fetal ovaries to identify and isolate novel GREL (gonadal ridge epithelial-like) cells from fetal ovaries. A stromal stem cell niche in adult ovaries is also described.
- > Demonstration of the remarkable effects of seminal fluid on the cervical immune response in women. Analysis of cervical biopsies taken before and after coitus by Sarah Robertson and her team showed that seminal fluid influences gene expression in the human female reproductive tract in a manner consistent with activating immune tolerance and promoting reproductive success.
- > Discovery of the widespread differential effects of maternal and paternal genomes on specific fetal muscles that indicate complex roles of imprinted genes with



different imprinting patterns in fetal muscle development. The results of Stefan Heindleder and colleagues indicate that the imprinted maternally expressed long non-coding RNA H19 is a major regulator of fetal muscle mass.

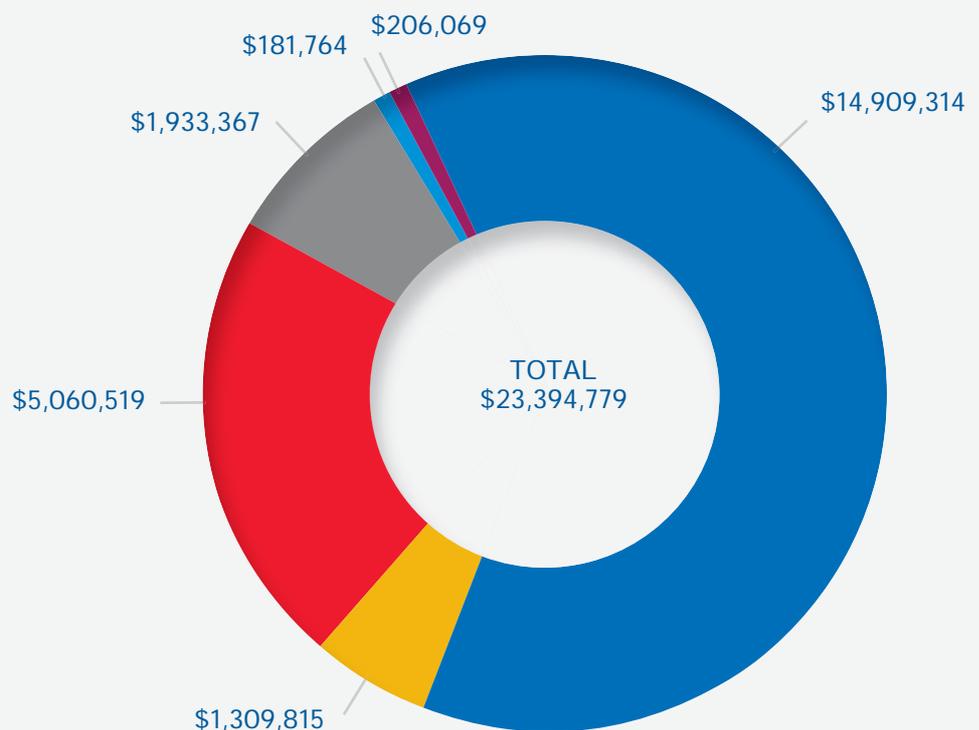
- > Advanced our understanding of the causes of cerebral palsy through the first finding of inherited copy number genetic variations in 20% of cerebral palsy cases and the discovery of multiple de novo candidate mutations on exome sequencing. This novel and important finding implies that cases of CP have a genetic basis.
- > Identification of major birth defects associated with different types of assisted reproductive technology. In the most comprehensive study of its kind in the world Michael Davies and colleagues compared the risk of major birth defects of the reproductive therapies commonly available internationally, including: IVF (in vitro fertilisation), ICSI (intracytoplasmic sperm injection) and ovulation induction. They also compared the risk of birth defects after fresh and frozen embryo transfer. The results were published in the *New England Journal of Medicine*.
- > Discovery of fundamental mechanisms of oocyte – cumulus cell communication. Darryl Russell and colleagues have shown that the oocyte secreted growth factor GDF9 interacts with extracellular matrix structures. Through this pathway, maternal hormones and the cumulus extracellular matrix modulate oocyte signalling to ovarian somatic cells. This insight has applications in improving assisted reproductive techniques.
- > Identification of genetic variants as well as their interaction with clinical and lifestyle factors that associate with pregnancy complications. Claire Robert's group have demonstrated that healthy diet and body weight protect from the adverse effects of key polymorphisms linked with preeclampsia, intrauterine growth restriction and preterm delivery.
- > Discovery of a novel role for haemoglobin within maturing oocytes. Jeremy Thompson and his team made the surprising observation comparing the transcriptome of cumulus cells following in vitro and in vivo maturation, implicating haemoglobin in supporting optimal oocyte development.
- > Demonstration that cumulus-oocyte complexes in ovulating ovaries adopt transient highly invasive capacity. This finding by Darryl Russell's team provides new insight into the mechanism of ovulation and is the first explanation of exactly how cumulus cells mediate oocyte release. This new understanding opens new avenues for investigating infertility.
- > Demonstration that TGFβ1 is a critical gene in endometriotic lesion development. Louise Hull and colleagues provided proof-of-principle that targeting TGFβ1 signalling pathways in cells that support the survival of ectopic endometrium may be an effective therapeutic approach in women with endometriosis.
- > Discovery of compounds that can reverse the detrimental effect of obesity on embryos - this finding from Rebecca Robker's group will be built upon to improve embryo development and pregnancy rates in agriculturally important species which have prevalent infertility, such as dairy cows, and may ultimately have utility in improving clinical outcomes in affected women.
- > Explanation of the mechanism by which the oocyte-secreted growth factors GDF9 and BMP15 interact to yield potent synergistic effects on ovarian somatic cells. Rob Gilchrist and David Mottershead have completed complex protein chemistry studies to show unexpectedly potent heterodimers have a key role in oocyte-cumulus cell complexes.

- > Exposition of co-evolution of the male external genitalia and vagina and cervix of female in rodent. Bill Breed and colleagues have found evidence for co-evolution of sperm design and structure of the egg coat, the zona pellucida.
 - > Characterisation of extracellular matrix regulation during development of reproductive tumors. Carmela Ricciardelli and colleagues have used genetic mouse models to show that ADAMTS1 is essential for mammary tumor growth and progression to metastasis, highlighting this enzyme as a potential therapeutic target to prevent metastatic disease.
 - > Demonstration that epithelial cell-derived TGFβ1 is essential for mammary gland remodelling. Wendy Ingman and her group have shown that both epithelial cell turnover and local macrophage phenotype are altered when this cytokine is deficient. These diverse roles of TGFβ1 in the mammary gland are likely to impact breast cancer risk.
 - > Completion of immunisation trials to evaluate: Meningococcal B vaccine trial in adolescents and adults, the effectiveness of the maternal influenza vaccination, and to assess the safety and immunogenicity of a booster pertussis (whooping cough) vaccination at 18 months of age. Helen Marshall and colleagues also trialled an educational intervention to improve uptake of human papillomavirus (HPV) vaccine in schools.
 - > Discovery of the utility of measuring the thickness of the aorta in relation to the renal changes in children with type 1 diabetes. This is a significant finding by Jenny Couper and colleagues who are part of the international Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AddIT) trial.
 - > Successful completion of the the design and development of a new innovative web-based intervention – ‘mums’ etalk’ (www.mumsetalk.com.au) to be used in the New Technology for New Mums research project which aims to improve the health and wellbeing of mothers and infants during a child’s first two years of life.
 - > Discovery of the role of 14-3-3 zeta in neurodevelopment and neuropsychiatric disorders. Quenten Schwarz and colleagues will now use this model to explore the associations between 14-3-3 zeta levels and schizophrenia in humans to develop targeted diagnosis and treatment.
 - > Demonstration that colonoscopy is the preferred mode of screening for colorectal cancer in kidney transplant recipients. Toby Coates and colleagues published this work in the British Medical Journal, which included an editorial piece.
 - > Demonstration that teenagers who had been born preterm showed relatively low brain plasticity in association with abnormally low levels of salivary cortisol, affecting learning and memory abilities.
- Julia Pitcher and colleague Michael Ridding also showed that being born even modestly preterm is associated with a reduced brain response.
- > Demonstration that maternal treatment with growth hormone can improve function of the placenta, the maternal supply line to the fetus, and improve fetal growth and survival, suggesting that methods to enhance maternal growth hormone may be beneficial in fetal growth restriction. Julie Owens and colleagues have also shown that neonatal treatment with a GLP-1 analogue that promotes insulin production and influences appetite control can prevent obesity onset in the young who were growth restricted. These outcomes are providing potential therapeutic approaches to overcoming early life programming of the major non-communicable diseases of our time, obesity and diabetes.
 - > Explanation of the risk for unborn children when asthma is not managed during pregnancy. To address this Vicki Clifton and colleagues also launched the first Australian trial of a dedicated asthma service for pregnant women.

Financials

Categories

- NHMRC
- ARC
- Government and public sector
- Industry
- Donations and philanthropic foundations
- Robinson Institute Foundation's



The financial information presented is for the Robinson Institute department only, and therefore exclude research income earned directly by our members. Further information on income of our members can be found throughout the Annual Report.

Funding highlights

During 2012 the Robinson Institute continued to successfully attract funds from major funding bodies to support research projects. Just some of the highlights are outlined below.

NHMRC

The National Health and Medical Research Council awarded Robinson Institute members more than \$11.2 million for projects and fellowships commencing in 2013. Major project grants include:

\$1,710,437 to Professor Jodie Dodd

Metformin and dietary advice to improve insulin sensitivity and promote gestational restriction of weight in pregnant women who are obese.

\$802,470 to Professor Mark Bartold

Comparison of periodontal ligament stem cells and induced pluripotent periodontal ligament stem cells for periodontal regeneration.

\$651,627 to Professor Sarah Robertson

Male-female sperm signalling - a novel pathway for peri-conceptual health.

BioInnovationSA

Dr Louise Hull was awarded \$97,000 in commercial funding from BioInnovationSA to develop a plasma diagnostic test for endometriosis.

Cancer Council and SAHMRI

The Cancer Council awarded Dr Claudine Bonder \$99,891 for a new target to combat breast cancer, and \$95,000 for a new molecule involved in the development of blood vessels within tumours.

In addition, the Cancer Council and the South Australian Medical Research Institute (SAHMRI) jointly awarded Professor Andrew Zannettino \$99,171 to investigate whether modifying the bone marrow stromal microenvironment alters the disease course of multiple myeloma.

Cancer Australia and Leukaemia Foundation

Professor Andrew Zannettino was awarded \$528,666 (2012-14) to determine if elevated N-cadherin expression is a poor prognostic indicator in multiple myeloma patients.

Captain Courageous

Professor Richard D'Andrea was awarded \$85,000 from Captain Courageous for dissecting the blood cell defect in Diamond Blackfan Anaemia.

Channel 7 Children's Research Foundation

Members were awarded more than \$550,000 from the Channel 7 Children's Research Foundation for projects commencing over 2012/2013; including \$75,000 to Associate Professor Leonie Heilbronn to determine if IVF impairs insulin sensitivity. Associate Professor Domenic Wilkinson was also awarded \$60,000 to understand the impact of a parent handbook for end-of-life decisions in critically ill children.

Diabetes Australia Research Trust

The Diabetes Australia Research Trust awarded more than \$260,000 for research into diabetes, including \$145,000 to Professor Julie Owens to identify epigenetic pathways from maternal obesity to type 2 diabetes in offspring.

Gardiner Foundation

Associate Professor Jeremy Thompson and Dr Rebecca Robker were awarded \$60,000 from the Gardiner Foundation for improving the fertility of high performance Holstein cows during early lactation.

Inner Wheel

Simon Barry was awarded a \$65,000 research grant from Inner Wheel.

National Breast Cancer Foundation

Associate Professor Wendy Ingman was awarded \$199,997 (2013-14) from the National Breast Cancer Foundation for a novel concept relating to parity-induced breast cancer protection.

National Heart Foundation

Dr Claudine Bonder was awarded \$130,000 from the National Heart Foundation for the development of a novel gene and cell therapies for pulmonary hypertension and Professor Stephen Worthley was awarded a \$16,980 Simpson Equipment Grant.

Novartis

Associate Professor Helen Marshall was awarded \$145,000 (2011-12) from Novartis to research the impact of invasive Meningococcal Disease in Australian children, to understand community knowledge and attitudes towards meningococcal disease and its prevention and values, views and preferences for immunisation programs.

Pfizer

Pfizer awarded more than \$220,000 (2012-13), including \$100,000 to Associate Professor Helen Marshall to assess the safety, tolerability and immunogenicity of a Meningococcal Serogroup B Recombinant Lipoprotein (rLP2086) Vaccine Given in Healthy Subjects Aged ≥ 11 to < 26 Years. \$50,000 was awarded to Professor Jenny Couper for research into incretin release and post prandial glycaemia in cystic fibrosis related diabetes.

South Australia Cancer Research Collaborative, Medvet and Community donor

Professor Andrew Zannettino, Professor Richard D'Andrea, Associate Professor Ian Lewis and other collaborators were awarded \$980,000 (2012-2013) for the South Australian Blood Cancer Tumour Bank.

Women's and Children's Research Foundation

Members were awarded more than \$190,000 in project grants. Dr Linda Wu received \$50,000 for reversing the detrimental effects of obesity on early embryo growth. Associate Professor Michael Stark was awarded \$50,000 for cerebral and systemic blood flow and oxygen kinetics during transition to predict early brain injury in very preterm infants. Ms Gai McMichael received \$49,913 for the genetic determinants of cerebral palsy and Dr Martin Donnelley was awarded \$43,754 for understanding the clearance of inhaled lead dust in the conducting airways using synchrotron imaging.

Fellowships and Awards



Dr Kylie Dunning

ARC

Commencing in 2012

Discovery Early Career Research Award

Dr Kylie Dunning

ARC Future Fellow

Dr Cheryl Shoubridge (School of Paediatrics and Reproductive Health): Understanding the molecular mechanisms of intellectual disability

Awarded in 2012

ARC Future Fellow

Professor Leonie Heilbronn (School of Medicine) - Examining the links between obesity and insulin resistance

NHMRC

Commencing in 2012

Early Career Biomedical Fellowship

Dr Tod Fulston

Senior Research Fellowships

Dr Rob Gilchrist and Professor Claire Roberts

Awarded in 2012

Senior Research Fellowships

Associate Professor Vicki Clifton, Dr Michelle Lane and Associate Professor Mark Nottle

Principal Research Fellowship

Professor Stan Gronthos

Career Development Fellowship

Dr Alice Rumbold

R.D.Wright Biomedical Research Fellowship

Dr Rebecca Robker

Early Career Research Fellowship

Dr Kerrilyn Diener

Other Fellowships

Florey Medical Research Foundation Fellowships

Veronika Sacco Clinical Cancer Research Fellowship: Dr Jacqueline Noll

Early Career Postdoctoral Northern Health Research Fellowship: Dr Annette Osei-Kumah

Mary Overton Fellowship, Royal Adelaide Hospital Research Foundation

Dr Kate Vandyke, Dr Agnes Arthur (awarded 2012)

MS McLeod Postdoctoral Fellowships

Dr Jemma Anderson, Dr Shiree Perano, Dr Martin Donnelley (awarded 2012)

Women's and Children's Health Foundation Early Career Award

Dr Linda Wu (commenced 2012)

Faculty of Health Science Student Travelling Fellowship

Kylie Ellis

Awards and prizes 2012

Adelaide International Scholarship

Sultana Khoda

Adelaide Neuroscience Research Travelling Scholarship & School of Physiology Travel Grant

Kylie Ellis

Australian and New Zealand Society of Respiratory Scientists

Associate Professor David Parson was awarded the Research Medal and inducted as a Fellow

Australian Society for Medical Research

Wai Sun awarded 'best of the best' poster prize

Associate Professor Wendy Ingman was a Leading Light Finalist

Professor Sarah Robertson was selected to present the AWT Edwards Oration

Australian Society of Periodontology

Professor Mark Bartold was awarded the RG Williams Memorial Prize for outstanding contributions to periodontal research

ASH Abstract Achievement Award

Professor Richard D'Andrea awarded the ASH Abstract Achievement Award for 'Shahrin NH, Brown AL, Diakiw S, and D'Andrea RJ. Investigation of KLF5 Function in Normal Hematopoiesis. Blood (ASH Annual Meeting Abstracts), Nov 2012; 120: 2313'

BUPA Health Foundation

Dr Pallave Dasari finalist for the Emerging Health Researcher award

Cardiac Society of Australia and New Zealand (CSANZ)

Dr James Richardson was a finalist for the Ralph Reader Presentation Award, Cardiac Society of Australia and New Zealand (CSANZ) for his work on the 'impact of timing and dose of mesenchymal stromal cell therapy in a preclinical model of acute myocardial infarction'

Channel 7 Research Foundation

Sam Buckberry awarded Channel 7 Children's Research Foundation postgraduate scholarship

Endocrine Society of Australia Travel Awards

Natalie Aboustate, Zainab Ali, Himawan Harryanto, Dr Nicolette Hodyl, Ezani Jamil, Hong Liu, Dr Annette Osei-Kumah, Amy Wooldridge

Faculty of Health Sciences

Wai Sun awarded poster prize
Dr Luke Schneider awarded the International Conference Award

Alison Care, Jesia Berry, Oana Maftai, Dr Prabha Andraweera and Jimin Xiong awarded the Dean's Commendation for Doctoral Thesis Excellence

Jesia Berry awarded the School of Population Health Award Best Thesis

German Academic Exchange Service Research Grant for Doctoral Candidates and Young Academics and Scientists

Mitchell Goldsworthy

International Society for Pharmacoeconomics

Dr Luke Grzeskowiak received the ISPE Scholarship Travel Award

Order of Australia

Professor Ross Haslam for distinguished service to medicine, particularly as a leader in the specialities of perinatology and neonatology, to professional development, and to medical research and education

Perinatal Society of Australia and New Zealand

Emeritus Professor Alistair MacLennan was awarded honorary life membership

Public Health Association of Australia's 2012 Population Health Congress

Jessica Reid

Research Career Development Network

Dr Martin Lewis awarded International Travel Award: MicroRNAs Europe 2012

Robinson Institute

Professor Sarah Robertson awarded the Robinson Institute Director's Award

SA Health 2012 Ministers Innovation Award

Dr Richard Sprod and the Centre for Education and Training Digital Media Unit, Women's and Children's Health Network: Learning Together: Innovations in patient education and support

School of Paediatrics and Reproductive Health

Dr Rob Gilchrist awarded for excellence in postgraduate supervision

Dr Lisa Akison awarded the Graduate Student Award

Dr Kylie Dunning awarded the Early Career Researcher Award

Laura Watson awarded Best Basic Research Paper Award

Skeptic of the Year Award for Friends of Science in Medicine

Emeritus Professor Alastair MacLennan

Society for the Study of Reproduction (USA)

Dr Rebecca Robker awarded the Young Scientist Award to represent the Society for the Study of Reproduction (USA) at the International Congress of Animal Reproduction, Vancouver Canada

Society of Reproductive Biology

Dr Melanie McDowall was a finalist in the 2012 New Investigator Award

Society for Reproductive Biology Travel Awards

Dr Lisa Akison, Peck Yin Chin, Jessica Laurence, Sam Buckberry



Mitchell Goldsworthy

Teratology Society Student Travel Award

Dr Luke Grzeskowiak awarded the Student Travel Award

Transplantation Society of Australia and New Zealand (Clinical)

Dr Michael Collins awarded the President's Prize

The University of Adelaide

Dr Louise Hull awarded the Professor Derek Frewin AO Citation for Clinical Teaching

Emily Bain awarded Medal for Honours Thesis

Dr Samuel Sidharta and Dr Tim Baillie awarded the University of Adelaide Postgraduate Award

Mitchell Goldsworthy awarded the Adelaide Research Abroad Scholarship and the AUGU RC Heddle Award

Underworks Millennium Type 2 Award

Professor Julie Owens winner of the Underworks Millennium Type 2 Award for 'Identifying epigenetic pathways from maternal obesity to type 2 diabetes in offspring'

University of South Australia

Dr Luke Grzeskowiak –awarded the School of Pharmacy and Medical Sciences Postgraduate Medal for most outstanding PhD thesis

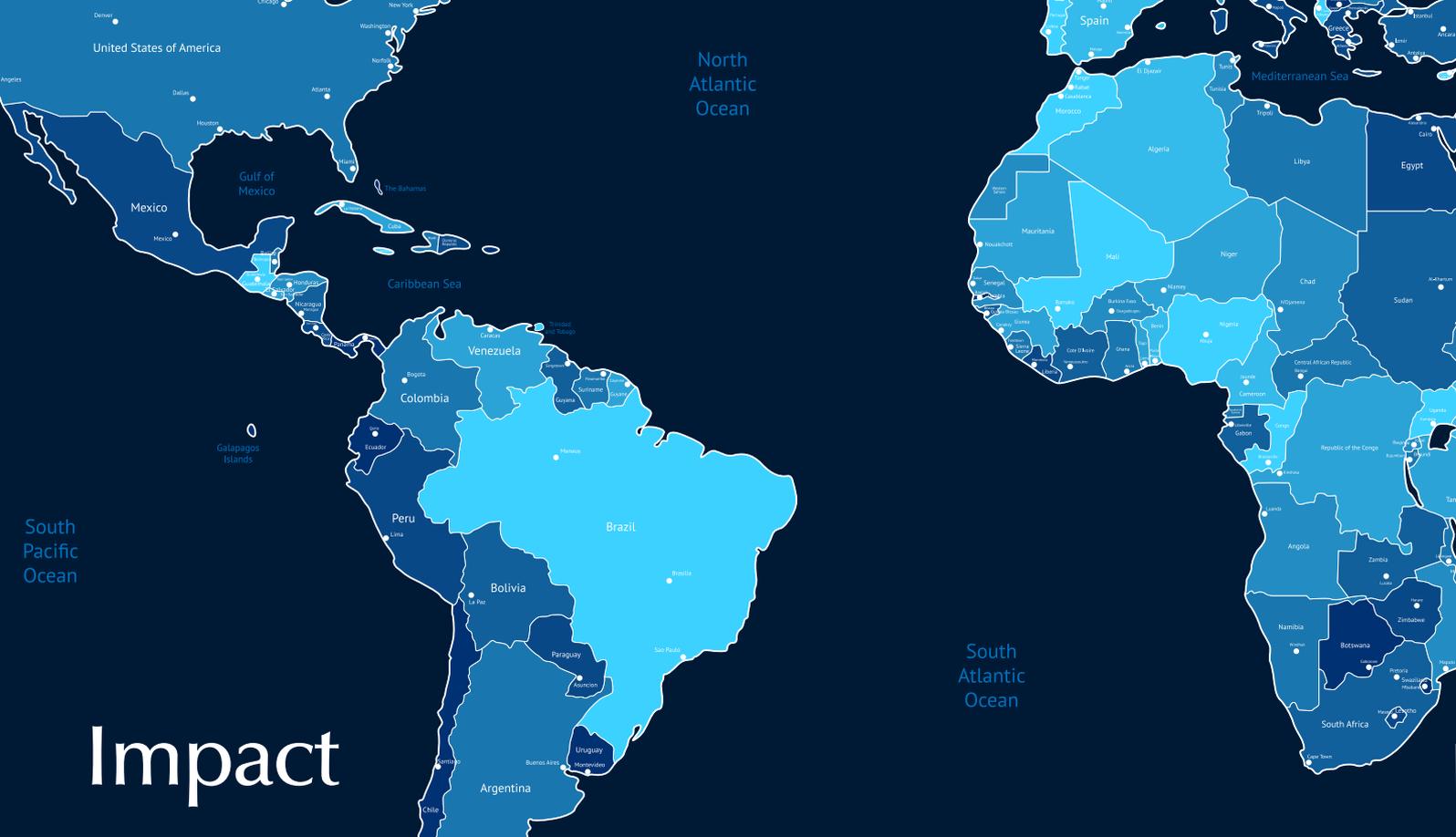
University of Leuven, Belgium

Associate Professor Taher Omari was awarded the title of Visiting Professor for his long standing collaboration with the Translational Research Centre for GI Disorders

Young Investigator Award

Dr Natasha McInnes winner of the 2012 WCH Foundation Young Investigator of the Year Award and People's Choice Award for her discovery of a gene that fights breast cancer and helps to keep cells healthy

Finalists: Dr Michael O'Callaghan, Dr Kristie Lee



Impact

Key Collaborations

Hospitals

The Robinson Institute and its research Centres are firmly embedded within South Australia's public health system. Robinson Institute members occupy a physical presence and conduct important collaborative research projects in the state's key hospitals, including the Women's and Children's, the Lyell McEwin, The Queen Elizabeth, Modbury and the Royal Adelaide. The unique and diverse affiliations we enjoy in these institutions ensure our scientists and clinicians are integrated with South Australia's medical practice, play a role in shaping effective health policy and can access clinical material as appropriate.

SA Pathology and Hanson Institute

The Robinson Institute has a strong link to SA Pathology and the Hanson Institute through the Centre for Stem Cell Research.

Cook Medical

The Robinson Institute is at the core of an important collaborative relationship that exists between the University of Adelaide and Cook Medical, a world leader in the production of reproductive technologies and products. One of the most successful of these is the Cook Medical Adelaide Fellowship. Other joint research projects focus on the improvement of reproductive technologies.

Jean Hailes Foundation for Women's Health

The Robinson Institute collaborates with the Jean Hailes Foundation for Women's Health through the National Alliance on Polycystic Ovarian Syndrome (PCOS). This unique initiative brings together multidisciplinary clinicians, women with PCOS, researchers and government representatives. The National Alliance on PCOS is designed to provide a single voice for polycystic ovarian syndrome, and has agreed on a vision to improve the lives of Australian women with PCOS through education, research and evidence-based health care.

Institute for Photonics and Advanced Sensing

In 2010, the Robinson Institute began collaborating with the University of Adelaide's Institute for Photonics and Advanced Sensing to develop new technologies to advance reproductive health research and practice. This followed a successful grant from the Premier's Science and Research Fund from the South Australian Government of \$700,000. The project was ongoing throughout 2012.

Fertility clinics

Robinson Institute members occupy a key presence in clinical practice and research development at two leading fertility clinics in Adelaide: Repromed and Fertility SA.

Women's and Children's Health Research Alliance

The Robinson Institute is party to an ongoing discussion between the Women's and Children's

Hospital, Women's and Children's Hospital Foundation, Women's and Children's Health Research Institute, SA Pathology, and other research groups at the Women's and Children's Hospital. This alliance seeks to improve the research outcomes on the site by ensuring appropriate research facilities and collaborations.

Fertility Coalition

The Robinson Institute is a founding partner in The Fertility Coalition, which was established in 2011 to launch the Your Fertility campaign. Additional partners include the Victorian Assisted Reproductive Treatment Authority (VARTA), Jean Hailes for Women's Health and Andrology Australia. This ongoing campaign aims to provide accurate, evidence-based information about fertility to people who want to have children. The Coalition is supported by funding from the Australian Government Department of Health and Ageing under the Family Planning Grants Program. For more information visit www.yourfertility.org.au

South Australian Health and Medical Research Institute (SAHMRI)

The Robinson Institute is involved in ongoing discussions with SAHMRI regarding an alliance and contribution to the *Health Mothers, Babies and Children* research theme.

Universities

The Robinson Institute collaborates with numerous national and international universities.



North Pacific Ocean

Presentations and speaker invitations

In 2012 members of the Robinson Institute delivered more than 250 presentations nationally and internationally. Of these, more than 65 were invited speakers.



International Visitors

The Robinson Institute welcomed many distinguished international researchers and students for collaboration, conferences, seminars and exchange programs throughout 2012. These interactions provided great experiences for our visitors and Institute members, particularly through the sharing of knowledge and expertise.

Visitor	Affiliation	Country
Valentina Basoli	University of Sassari, Sardinia	Italy
Dr Joe Brierley	Great Ormond St Hospital	England
Professor Oliveira Bruni	University of Rome	Italy
Livia Cabitta	University of Sassari, Sardinia	Italy
Professor Angela Clow	University of Westminster	England
Professor Lelia Duley	University of Leeds	England
Professor Rafael Ferri	Department of Neurology I.C. and Sleep Disorders, Troina	Italy
Professor Jayne Garland	University of British Columbia	Canada
Professor William Giannobile	University of Michigan	USA
Professor Matthew Gillman	Harvard Medical School/Harvard Pilgrim Health Care Institute, Harvard University	USA
Mr Robin Law (PhD student of Prof. Clow)	University of Westminster	England
Professor Debbie Lawlor	University of Bristol	England
Professor Annette La Greca	Department of Psychology, University of Miami FL	USA
Dr Bruce Lessey	University of South Carolina and Clemson University	USA
Ms Catherine Lowenhoff	Churchill Fellowship	England
Professor Robert Mittendorf	University of Loyola, Chicago	USA

Visitor	Affiliation	Country
Professor Leslie Myatt	University of Texas, San Antonio	USA
Professor Richard Oko	Queens University, Kingston Ontario	Canada
Dr Viv Perry	University of Nottingham	England
Professor Lucilla Poston	Kings College London	England
Dr Syede Raza	Neurotoxicology Lab, Department of Toxicology, Jamia Hamdard University, New Delhi	India
Dr Mike Robling	Co-Director, South East Wales Trials Unit, Cardiff University, School of Medicine	Wales
Professor Nathalie Rommel	University of Leuven	Belgium
Professor John Rothwell	Institute of Neuroscience, University College London	England
Professor Mariano Sanz	University Complutense of Madrid	Spain
Professor Julian Savulescu	University of Oxford	England
Dr Satoshi Sugimura	National Livestock Breeding Center	Japan
Dr Merryn Voysey	University of Oxford	England
Associate Professor Haitao Zeng	Sun Yat Sen University, Guangzhou	China
Dr Ren Zi	Sun Yat Sen University, Guangzhou	China

Community Engagement

Healthy Development Adelaide

Healthy Development Adelaide (HDA) plays a key role in uniting research, clinical, end-user and affiliated communities through linking research, service delivery and policy development in South Australia. Through these linkages, HDA promotes, facilitates and enables multidisciplinary research that advances understanding of healthy development and ensures the physical, psychological and social health of infants, children and adolescents.

HDA was established in 2004 as an initiative of the University of Adelaide, and is led by Professor Robert Norman (Director Robinson Institute, University of Adelaide), Professor Michael Sawyer (Women's and Children's Health Network / University of Adelaide) and Professor Claire Roberts (Robinson Institute, University of Adelaide).

HDA is supported by a partnership of South Australian organisations that includes the Robinson Institute, Channel 7 Children's Research Foundation, University of South Australia, Flinders University, Department for Education and Child Development, Fertility SA, Repromed, Women's and Children's Health Research Institute and Flinders Fertility.

HDA has over 205 research members (senior researchers, early career researchers and postdoctoral students) and over 305 associate (non-research) members. The membership base is drawn from the University of Adelaide, University of South Australia, Flinders University, relevant institutions (local, national and international), government, and the general community.

For more information, visit adelaide.edu.au/hda

HDA Events

Each year HDA delivers a series of public events across a broad range of topics. The aim is to communicate important multidisciplinary health information, as well as provide opportunities for networking and research collaborations. The events are well attended by a diverse audience including researchers, students, government, health service personnel and educators, organisations, teachers and the general community. From 2005-2012, 77 events have been held with more than 9,500 attendees.



(Left to right) Professor William Ledger, Professor Rob Norman, Leigh McLusky, Dr Christine Kirby, Professor Andrew Dutney and Associate Professor Jane Halliday celebrating 30 years of IVF in South Australia

2012 events

8th annual HDA Oration

> Women, empowerment and health for all

The evening was chaired by HDA Co-Convenor Professor Robert Norman (Director Robinson Institute), who presented Professor Vivienne Moore (Robinson Institute) with the 2012 Healthy Development Adelaide Award. Professor Moore's presentation offered an exciting and profound overview of improving women's health through empowerment, women's reproductive choices, lifestyle issues, managing children's health and wellbeing, and the role of men within this framework.



Professor Vivienne Moore accepting her award from Professor Rob Norman (left) and Professor Michael Sawyer (right)

HDA Thematic Evenings

> Social media for kids: to tweet or not to tweet?

> Connecting with children in need

> Are they keeping you up? sleep: from infancy to adolescence

> Tackling men's health and fertility

These thematic evenings were co-sponsored by the Robinson Institute and the Fertility Coalition as part of My Fertility Week. Speakers included: Professor Sarah Robertson (Robinson Institute), Dr Hassan Bakos (Repromed), and Professor Robert McLachlan (Prince Henry's Institute).

HDA Collaborative Events:

> Developmental Overnutrition: an old hypothesis with new relevance?

With the Robinson Institute, the School of Population Health and Clinical Practice, University of Adelaide and Professor Debbie Lawlor from the University of Bristol.

> Scientific Networking Event & Speed Networking Session

With the Australian Society for Medical Research (ASMR – SA Branch), Professor Claire Roberts (Robinson Institute), Jen Clark (University of Adelaide), Professor Ross McKinnon (Flinders University) and Dr Natalie Parletta (University of South Australia).

> Science in the Cinema: In Time

With the Australian Society for Medical Research (ASMR – SA Branch).

> Babies and Bugs: what's going on in baby's gut?

With the Nutrition Society of Australia (SA Branch) and Professor Sharon Donovan (University of Illinois). The talk was followed by a special 'Meet the Professor' session that included 15 undergraduate and postgraduate students.

> Celebrating 30 years of IVF in South Australia

To celebrate the significant advancements in IVF over the last 30 years, the Robinson Institute hosted this event with support from Fertility SA and Flinders Reproductive Medicine. Sponsors included MSD and Merck Serono Australia.

Speakers included Professor Rob Norman (Director Robinson Institute), Professor William Ledger (IVF Australia), Associate Professor Jane Halliday (Murdoch Children's Research Institute), Professor Andrew Dutney (Flinders University) and Dr Christine Kirby (Repromed).

Research Symposium

In 2012 the inaugural Robinson Institute Research Symposium was held at the National Wine Centre in Adelaide. The full day event brought together Robinson Institute research and professional communities to learn more about the great work being undertaken across the Institute, and gave members the opportunity to network.

The program featured presentations from senior and mid-career researchers. The audience was able to hear the value of the Institute's work through a patient experience study. Rebecca Lawson-Cook generously gave her time and openly shared her and daughter Eliza's journey. Eliza was born very preterm, at just 25 weeks. This amazing story touched the hearts of all and inspired members to continue and advance their life saving research.

The Robinson Institute's honours and postdoctoral students and early career researchers also shared their research through a poster display and competition. The winners were Tod Fulston, Noor Lokman and Natasha McInnes.

The Robinson Institute Directors Award and Jeffrey Robinson Honours Scholarship were also presented. Professor Sarah Robertson received the Director's Award for her outstanding research and leadership, particularly her commitment to the Reshaping the Robinson project. The Jeffrey Robinson Scholarship was awarded to Katherine Watson, an exceptional student interested in menstrual disorders and reproductive immunology. To hear more about Katherine's experience see page 107.

Right: Professor Rob Norman and Director's Award winner Professor Sarah Robertson
Below: Rebecca Lawson-Cook sharing her experience



“ The audience was able to hear the value of the Institute's work through a patient experience ”



Dr Julia Pitcher, Associate Professor Michael Stark, Luke Schneider, Ann-Maree Vallence and Mitchell Goldsworthy



Sophie Porter, Sarah Turner, Rachel Kontic, Sarah Walsh and Imogen Craig

Your Fertility

The choice to have a family is important for most Australians. For many individuals and couples however, having a baby is not easy to realise. The Your Fertility project was launched in 2011 to increase knowledge and awareness about fertility in the community. Delivered through the Fertility Coalition - a partnership between the Robinson Institute, the Victorian Assisted Reproductive Treatment Authority (VARTA), Andrology Australia and Jean Hailes for Women's Health - the project uses the latest evidence to inform individuals and couples who wish to have a baby.

By sharing the latest information, Your Fertility aims to empower people to make informed and timely decisions regarding their

reproductive health. Importantly, it covers key lifestyle factors for both women and men, including age, weight, smoking and alcohol.

"Traditionally we have focussed on the health of the female when trying to have a baby," says Professor Robert Norman, Director Robinson Institute.

"But we now know that 40% of infertility cases are due to the man, and that age is a major factor."

Your Fertility aims to share such vital information so that people can effectively plan for the best pregnancy outcome.

"It is important that couples are aware of the risks involved with all lifestyle factors, particularly those that can be lessened. For example, women who smoke are more likely to be infertile than non-smokers."



Since launching the project in 2011, Your Fertility has been a great success. The website and the project launch are estimated to have reached nearly five million people. The resources continue to grow, including video case studies from experts and real life fertility stories. The website also features the Your Fertility quiz and blog.

For more information, visit yourfertility.org.au



I'm a Scientist, Get Me Out of Here!

I'm a Scientist, Get me Out of Here is an award-winning science enrichment and engagement activity, now in its third year in Australia. Scientists and students talk online through the I'm a Scientist website. Students vote for their favourite scientist, then those with the least votes are dismissed one by one until a single winner remains. In 2012, Robinson Institute reproductive biologist Dr Hannah Brown entered the competition and was the winner in the 'Organs Zone'. For Hannah this was an amazing honour and fantastic experience.

"It was an absolute honour to be part of I'm A Scientist, and an even greater one to win," says Hannah.

The competition ran online for two weeks. During the first week the scientists participated in online chat sessions where the children asked science-related questions. In the second week the evictions began.

"It was two full-on weeks of science communication but it was great fun. The kids asked a range of questions on topics from space to evolution, so I really had to think on the spot," says Hannah.

The most rewarding part of the journey for Hannah was not just winning the competition, but being able to use her \$1,000 prize money to further engage with students from Challa Gardens Primary School. Hannah led two 90 minute in-school sessions focussing on 'what a scientist looks like' and 'endangered species preservation' - which included the Panda Breeding Program at the Adelaide Zoo. To bring these sessions to life she took 60 Year 6 and 7 students to the Adelaide Zoo, covering the entire costs for the day.

"The students had a fantastic time on the excursion. We followed the endangered species trail and completed a handbook prepared by the teachers and myself, making it a valuable educational experience.

"Dr Kylie Dunning and Dr Emily Alvino from the Robinson Institute also volunteered their time as scientist mentors for the day."

I'm a Scientist is a great way for researchers to engage with the community, and to inspire the next generation.

Visit imascientist.org.au for more information.

Science Stories

In 2012 the Robinson Institute launched Science Stories - a monthly online publication which provides insight into some of the top papers published by Institute members. The stories capture personal anecdotes and an understanding of life as a scientist and/or clinician working to improve reproductive health, early origins of disease, the health of women and babies, and children and adolescents. The stories are written by science writer Sarah Keenihan, and are targeted at both a scientific and non-scientific audience. The Robinson Institute will continue to grow Science Stories in 2013.

Visit robinsoninstitute.edu.au/science-stories



Media Impact

Research leaders at the Robinson Institute made a strong impact in the media.

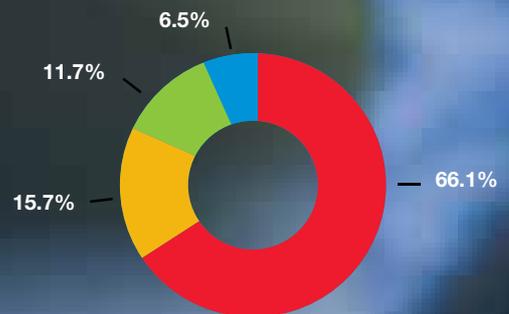
In 2012 the Institute reached more than 12 million people, with over 9 million reached through the press alone.

The media is an essential part of science communication. The Robinson Institute considers that one of the obligations of members is to share research outcomes so that the general public is better informed about reproductive and paediatric health choices.

In 2013, the Robinson Institute will continue to engage the media to share its ground-breaking research.

Social media offers many opportunities for communication and conversations between researchers and the general public. In 2012 the Robinson Institute established a Facebook page ([facebook.com/RobInstInstitute](https://www.facebook.com/RobInstInstitute)), a twitter account (@RobInstInstitute) and a YouTube channel ([youtube.com/robinsoninstitute](https://www.youtube.com/robinsoninstitute)) to allow further sharing of information and facilitate online conversations.

Media Type	#Appearances	Audience/circulation
Internet	418	879,528
Radio	99	523,600
Press	74	9,413,025
Television	41	1,344,000



Australian Research Centre for Health of Women and Babies

All over the world, the birth of a baby is one of the most significant life events for a woman and her family



Directors' report

The experience of pregnancy and events surrounding birth can have a profound impact on the health of women and children in the short and long term.

The Australian Research Centre for Health of Women and Babies (ARCH) is an international centre of excellence in maternal and perinatal research. Focused on women and their families, ARCH is committed to generating research evidence for translation into clinical practice and health policy.

Centre members are clinicians, trial coordinators, epidemiologists, scientists, statisticians and students working collaboratively to:

- > Address gaps in knowledge relating to maternal and perinatal health
- > Generate research evidence of the highest quality that promotes the best health possible for all women and their babies
- > Ensure that research findings are incorporated into health care practice
- > Increase capacity in research synthesis, randomised trials and implementation and translational research through career development and education
- > Strengthen existing collaborations and identify new international, national and regional collaborations



Research within ARCH encompasses the spectrum from preconception through pregnancy and childbirth, infancy and later life, and includes:

- > Preconception care
- > Nutrition to optimise health outcomes
- > Maternal health in pregnancy
- > Fetal growth and wellbeing
- > Intrapartum care
- > Postnatal health and wellbeing
- > Early childhood development related to maternal perinatal care
- > Developmental origins of health and disease

ARCH takes an integrated approach through:

- > Systematic reviews and research synthesis
- > Randomised clinical trials
- > Qualitative research
- > Short and long term follow up of research cohorts
- > Economic evaluations of different care options
- > Translation and implementation of research into practice

The research and translational capabilities of ARCH are reflected in strong collaborative research links with key international and national organisations in maternal and perinatal health. ARCH is the Australasian Satellite for the international Cochrane Pregnancy and Childbirth Group, supporting 350 review authors in Australia and New Zealand to prepare and maintain Cochrane reviews.

ARCH's profile in publications, collaborations and translation during 2012 continues to maintain the high esteem in which it is held in Australia and internationally. Results from ongoing studies including IDEAL, LIMIT, A*STEROID, DIAMIND, WISH and MAGENTA – which address research questions relating to the health of women and children – are generating health information to inform practice and policy beyond 2012.

Professor Caroline Crowther, Clinical Director
Philippa Middleton, Executive Director

Professor Caroline Crowther



International Maternal and Perinatal Health

Although childbirth is considered a relatively safe process in high-income countries, the same cannot be said for other societies. Statistics collected across the world show that women and babies in low-income countries have high rates of birth-associated morbidity and mortality due to preventable causes such as haemorrhage and infection. The International and Perinatal Health Group is committed to taking a global view on maternal and childhood health through conducting collaborative research activities to improve knowledge, build capacity and identify pathways for improved health outcomes after delivery. The Group has established strong links with colleagues in South East Asia and internationally through collaborating in international multicentre randomised trials, conducting individual participant data meta-analyses and providing

advice to the World Health Organization projects on maternal and fetal health.

During 2012 the Group worked across a diverse portfolio of projects, including:

- > Ongoing involvement in the SEA-URCHIN initiative (South East Asia – Using Research for Change in Hospital-acquired Infection in Neonates) to create implementation strategies for prevention of neonatal infection and improve clinical practice and health outcomes for babies
- > Ongoing participation in the Royal Australian and New Zealand College of Obstetricians and Gynaecologists initiative to train obstetric fellows from Indonesia
- > Assessment of how community-based support and development can improve maternal and child health in Pakistan
- > Development of international guidelines for management of postpartum haemorrhage

Group leader

Professor Caroline Crowther

Group members

Jodie Dodd, Melissa Ewens, Rosalie Grivell, Zohra Kamran, Philippa Middleton and Thach Tran

Research synthesis

Research synthesis: pioneering a powerful tool for presenting complex medical information

Improving the health of women and babies relies on having access to all the relevant evidence for a particular therapy or intervention. The Research Synthesis Group aims to conduct, promote and support the preparation and update of high quality systematic reviews of the existing clinical evidence relating to care of women and babies. Much of this work is conducted via the Group's capacity as the Australian Satellite for the international Cochrane Pregnancy and Childbirth Group, which supports nearly 300 Australian review authors in preparation and maintenance of Cochrane reviews. Other work advances the science of research synthesis through new methods and by addressing complex new topics.

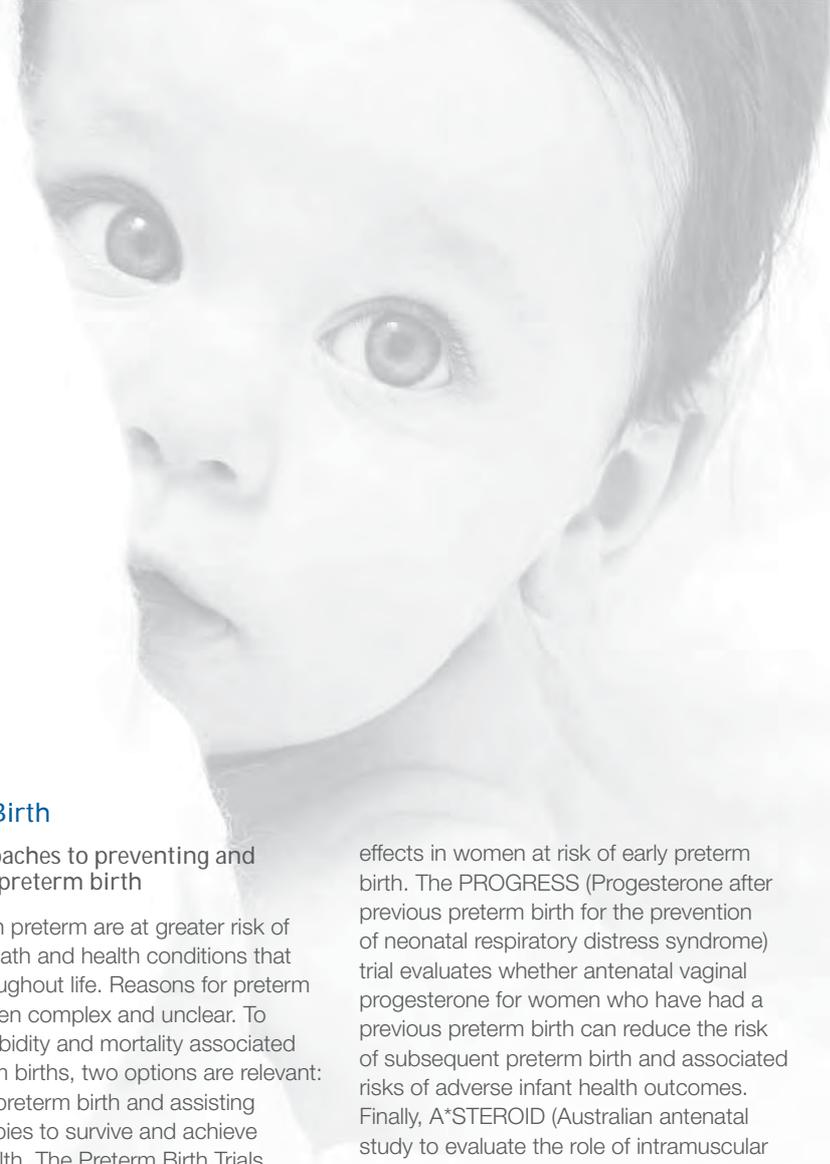
The Group was very active during 2012. With funding support from the NHMRC, the Group assisted Australian authors to produce one third of the world's Cochrane reviews in pregnancy and childbirth. The NHMRC also funded two important individual participant data meta-analyses – one analysing trials of antenatal magnesium sulphate for fetal, neonatal and infant neuroprotection (AMICABLE) and the other addressing trials of antenatal repeat doses of steroids (PRECISE). By the end of 2012, AMICABLE was at data analysis stage, and PRECISE was at data collection stage. Both analyses will clarify which groups of women/babies will benefit most from these effective interventions. The Group was also funded by AusAID to carry out a synthesis of 'Nutrition interventions and programs for reducing mortality and morbidity in pregnant and lactating women and women of reproductive age' during 2012.

Group leaders

Professor Caroline Crowther
Ms Philippa Middleton

Group members

Emily Bain, Claire Binnion, Tanya Bubner, Jodie Dodd, Rosalie Grivell, Shanshan Han, Emer Heatley, Zohra Kamran, Mary Paleologos, Elen Shute, Lisa Yelland and Sasha Zhang



Diabetes Trials

Clinical trials for preventing and treating gestational diabetes to optimise the health of mothers and their children

Diabetes in pregnancy can lead to short and long-term health problems for mothers and their children. Short-term outcomes include higher risk of pre-eclampsia, large babies and birth injuries. In addition, over half the women who experience gestational diabetes are at increased risk of subsequently developing type two diabetes within the following 10 years. Long-term poor health outcomes for children of mothers with gestational diabetes include increased risk of obesity and impaired development. The Diabetes Trial Group is focused on uncovering approaches to prevent and manage high blood glucose concentrations in pregnant and postpartum women for the future health of those mothers and their children.

In 2012 the Group completed recruitment for the IDEAL (Investigation of dietary advice and lifestyle for women with borderline gestational diabetes) randomised trial. Targeting pregnant women who have borderline glucose intolerance on screening for gestational diabetes, this trial addresses whether dietary and lifestyle advice given to such women reduces neonatal complications without increasing maternal risk. To fund IDEAL, the Group secured an NHMRC project grant. Women and their babies participating in the trial are now being followed up.

Starting in 2012, the Group is also conducting the DIAMIND (diabetes reminder) randomised controlled trial to determine whether an SMS text reminder system will significantly increase attendance for oral glucose testing by 6 months postpartum in women who have recently experienced gestational diabetes. The trial was designed to find ways to increase the number of women who are checked for elevated glucose readings after giving birth, in order to ultimately improve their long-term health.

Group leaders

Professor Caroline Crowther
Ms Philippa Middleton

Group members

Pat Ashwood, Daniela Gagliardi, William Hague, Shanshan Han and Emer Heatley

Preterm Birth

New approaches to preventing and managing preterm birth

Babies born preterm are at greater risk of neonatal death and health conditions that persist throughout life. Reasons for preterm birth are often complex and unclear. To reduce morbidity and mortality associated with preterm births, two options are relevant: preventing preterm birth and assisting preterm babies to survive and achieve optimal health. The Preterm Birth Trials Group identifies and tests interventions for both options, with outcomes measured not only in the neonatal period but also into childhood and the adult years. This long-term approach is critical to see the true impact on health for preventing and treating preterm birth.

During 2012 the Group focused on conducting and following up several trials addressing health of preterm infants.

Previous research has shown that antenatal magnesium sulphate offers fetal, neonatal and infant neuroprotection for very preterm babies. The NHMRC-funded multicentre randomised trial MAGENTA (Magnesium Sulphate at 30 to 34 weeks' Gestational age: Neuroprotection Trial) is now assessing whether similar short and long-term benefits (such as preventing cerebral palsy) occur at later gestational ages.

Three other trials recently completed recruitment, and two of these are now in long-term follow-up phase. The IRIS (Different Infusion Rates of Magnesium Sulphate Before Preterm Birth for Neuroprotection) trial assesses whether slower infusion of magnesium, compared with the standard rate, lessens adverse

effects in women at risk of early preterm birth. The PROGRESS (Progesterone after previous preterm birth for the prevention of neonatal respiratory distress syndrome) trial evaluates whether antenatal vaginal progesterone for women who have had a previous preterm birth can reduce the risk of subsequent preterm birth and associated risks of adverse infant health outcomes. Finally, A*STEROID (Australian antenatal study to evaluate the role of intramuscular Dexamethasone versus Betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability) is a large multicentre trial comparing two effective antenatal steroids for neuroprotection in preterm infants.

Group leaders

Professor Caroline Crowther
Ms Philippa Middleton

Group members

Pat Ashwood, Emily Bain, Vincent Ball, Jodie Dodd, Melissa Ewens, Daniela Gagliardi, Rosalie Grivell, Caroline Holst, Michaela Jarrett, Zohra Kamran, Ellen Lyrtzis, Mary Paleologos, Kaye Robinson, Jacqueline Smith, Thach Tran, Sophie Trenowden, Lisa Yelland and Yu Zhang

“ Although childbirth is considered a relatively safe process in high-income countries, the same cannot be said for other societies ”

Professor Jodie Dodd



Maternal Fetal Medicine

Evaluating health care interventions to improve outcomes in complicated and uncommon conditions of pregnancy

Maternal fetal medicine specialists provide expert diagnosis and ongoing care for women whose pregnancy is associated with significant complications, either for the woman or her unborn baby. Many of these conditions are rare and to investigate efficacy of care requires extensive collaboration with specialists both nationally and internationally. Fetal anaemia caused by red cell incompatibility is quite uncommon, and is estimated to occur in approximately 0.1 - 0.6% of all pregnancies. The group is currently evaluating whether ultrasound assessment of fetal cerebral blood flow velocity can be used to accurately time second and subsequent transfusions for women with red cell alloimmunisation, where her unborn baby is at risk of developing anaemia in-utero. Due to the uncommon nature of this condition, the Group collaborates with maternal fetal medicine specialists across Australia and around the world.

Group members

Senior Lecturer: Rosalie Grivell

Senior Trial Coordinator: Andrea Deussen

Clinical Researcher: Chad Anderson

Administrative Support: Jacqueline Smith

Statistics and Data Management Team: Lisa Yelland, Vincent Ball and Yu Zhang

Multiple Pregnancy

Evaluating the effect of timing of birth for women with a twin pregnancy at term

It is well recognised that multiple pregnancy increases the occurrence of health complications in both mothers and infants. Although women with a twin pregnancy are more likely to give birth preterm, approximately 46% are able to maintain pregnancy and give birth after 37 weeks of gestation. For women whose twin pregnancy continues beyond this point, risks of perinatal mortality and morbidity increase with advancing gestational age. In addition to experiencing elevated risk of poor health outcomes around the time of delivery, children born of multiple pregnancies are more likely to experience long-term problems such as cerebral palsy and developmental delay.

The Multiple Pregnancy Group consists of an extensive network of collaborators committed to undertaking studies to improve the health and wellbeing of mothers with a multiple pregnancy and their babies. Recently the Group conducted a multicentre randomised trial to evaluate the optimal time of birth for women with an uncomplicated twin pregnancy at 37 weeks' gestation. Recruitment was completed in early 2011. Infants are now aged 18 months - 2 years of age, and are being followed to monitor long-term health outcomes.

Group members

Clinical and Scientific Members: Caroline Crowther and Ross Haslam

Emeritus Member: Jeffrey Robinson

Trial Coordinator: Andrea Deussen

Statistics and Data Management Team: Lisa Yelland, Caroline Holst, Kaye Robinson, Vincent Ball and Yu Zhang

Obesity in Pregnancy

Evaluating the effect of overweight and obesity during pregnancy on maternal and infant health outcomes

The prevalence of overweight [Body Mass Index (BMI) 25.0-29.9kg/m²] and obesity [BMI >30.0kg/m²] is rising worldwide, affecting in excess of 110 million children, and 1.3 billion adults across the globe. The impact of maternal overweight and obesity during pregnancy and childbirth is substantial, and almost 50% of pregnant women in Western societies are entering pregnancy with a BMI above 25kg/m². There are well-documented risks of adverse health outcomes associated with obesity during pregnancy, and these risks increase as BMI rises. High maternal BMI during pregnancy is associated with a greatly increased risk of developing diabetes and cardiovascular disease in women. Furthermore, for the infant, high maternal BMI is a significant predictor of future child and adult obesity.

Research conducted by the Obesity in Pregnancy Group is focused on the evaluation of health care interventions during pregnancy on maternal, infant and early childhood health outcomes, including subsequent risk of obesity. To address these research goals, the Group has recently completed recruitment of more than 2,200 women who participated in a randomised trial evaluating the effect of dietary and exercise advice during pregnancy on maternal and infant health outcomes. This cohort of women and their infants – who are now 3 years of age – are being followed for monitoring of their growth, development and wellbeing.

Group members

Senior Trial Coordinator: Andrea Deussen

Research Dietician: Courtney Cramp

Research Assistants: Lavern Kannieappan, Angela Newman

Senior Lecturer: Rosalie Grivell

Postdoctoral Research Fellow: Lisa Moran

Emeritus Member: Jeffrey Robinson

Research Assistants: Dannielle Post, Caroline Sheppard, Meredith Kelsey and Stephanie Hendrijanto

PhD Students: Sui Zhixian, Tulika Sundernathan

Statistics and Data Management Team: Lisa Yelland, Caroline Holst, Vincent Ball and Yu Zhang

Research Support: Greg Beaumont, Jacqueline Smith

Scientific and Clinical Staff: Julie Owens, Anne MacPherson



Professor Bill Hague



Obstetric Medicine

Improving outcomes for pregnant women with medical complications

When medical problems arise during pregnancy, the health of both mother and baby is compromised both immediately and in the longer term. Developing sound clinical guidelines for the management of pregnancy complications relies on a collaborative approach to generate evidence.

The Obstetric Medicine Group is a world leader and collaborator in the development and performance of randomised controlled trials relating to problem pregnancies. The Group has already demonstrated that oral metformin is as safe and as effective as insulin injections in the treatment of women with gestational diabetes, and has supported the identification of appropriate blood pressure targets for women with hypertension in pregnancy.

In 2012, in collaboration with colleagues in The Netherlands, the Group completed and published data from the FRUIT (FRagmin in Utero-placental Insufficiency and Thrombophilia) trial. This trial was the first of its kind to demonstrate the benefit of anticoagulant injections with aspirin, compared with aspirin alone, for pregnant women with previous early onset pre-eclampsia and an inherited tendency to clotting, in the prevention of recurrent early-onset disease.

During 2012, the Group also conducted clinical trials exploring the use of folic acid to prevent preeclampsia, and the administration of metformin to prevent recurrent gestational diabetes.

Researchers have also continued to follow up the unique cohort of children and their mothers who had earlier participated in the

MiG (Metformin in Gestational Diabetes) trial of metformin (versus insulin) in the management of women with gestational diabetes. This trial has identified metformin as a potential in utero treatment for the prevention of childhood obesity.

In addition, recruitment was completed for the TIPPS (Thrombophilia In Pregnancy Prophylaxis Study) collaboration, addressing the safety and effectiveness of low-molecular-weight heparin for preventing placenta-mediated pregnancy complications and venous thromboembolism in women with thrombophilia.

Finally, recruitment for the CHIPS (Control of Hypertension In Pregnancy Study) collaboration was also completed. This study seeks to determine - for pregnant women with mild to moderate high blood pressure - the risks and benefits for mother and baby in controlling the mother's blood pressure more or less tightly during pregnancy.

Group members

Senior Clinical Trial Coordinator: Suzette Coat

Psychologist: Rachel Hughes

PhD Candidate: Mansi Dass Singh

Ms Philippa Middleton

Translational Health

Translating perinatal research results into action for improved health of babies

Medical knowledge often needs to be translated in order for it to make an impact on practice. The Translational Health Group works to promote evidence based practice in womens' and babies' health through the dissemination and implementation of research findings into practice and policy. Clinical practice guidelines are increasingly being applied to produce evidence-based recommendations for health professionals – and to guide implementation of these recommendations. Implementation science is a new approach that develops and evaluates strategies to facilitate translation of effective methods into changed practice. The Group has been appointed to the NHMRC Evidence Panel 'Providers with expertise relevant to the development and presentation of health advice'. Through this channel, the Group advises on antenatal care guidelines for the Australian Department of Health and Ageing, and on breast cancer for Cancer Australia. The Group is also developing bi-national guidelines on the use of steroids in pregnancy and contributing to development of the Screening, Diagnosis and Management of Gestational Diabetes in New Zealand Guideline.

The Group's major implementation project is WISH (Working to Improve Survival and Health for babies born very preterm). Through WISH, a grant from the Cerebral Palsy Alliance has allowed monitoring of the uptake of antenatal magnesium sulphate for fetal, neonatal and infant neuroprotection across all tertiary maternity hospitals in Australia and New Zealand. This approach has helped to change practice in Adelaide's Women's and Children's Hospital in 2012, where over 90% of eligible women received antenatal magnesium sulphate for the prevention of cerebral palsy.

Group members

Pat Ashwood, Emily Bain, Tanya Bubner, Caroline Crowther, Mary Paleologos and Sally Reid



Indigenous Maternal Perinatal Health

Working with indigenous organisations and communities to improve maternal and child health

Pregnancy and perinatal outcomes for Aboriginal women are relatively poor compared to the rest of the Australian population. Although many factors contribute to health inequality for indigenous mothers and babies, culturally appropriate care can help to close the gap. The Indigenous Maternal and Perinatal Health Group is committed to improving the health of Aboriginal women and their babies in the perinatal period.

In 2012, the Group was selected by the SA Women's and Children's Health Network to evaluate the SA Aboriginal Family Birthing Program. This program works as an equal partnership between Aboriginal maternal and infant care practitioners, trainees and midwives. This evaluation is due for

completion in early 2014. The Group also works closely with Associate Professor Stephanie Brown (Murdoch Children's Research Institute), who leads the NHMRC-funded Aboriginal Families Study.

This collaboration is documenting South Australian Aboriginal womens' experiences of services during pregnancy, childbirth and the first few months after giving birth.

Through the SA Aboriginal Family Birthing Program evaluation and the Aboriginal Families Study, the Group is looking at the health impacts for Aboriginal women and children of access to better quality, culturally-appropriate care. Early findings indicate that appropriate perinatal care is improving health and social outcomes for Aboriginal families.

Group members

Stephanie Brown, Tanya Bubner, Caroline Crowther, Karen Glover, Jessica Reid, Jeffrey Robinson, Alice Rumbold and Thach Tran

“ This program works as an equal partnership between Aboriginal maternal and infant care practitioners, trainees and midwives ”

Emeritus Professor Alastair MacLennan

Cerebral Palsy

Genetic susceptibility and epigenetic triggers for cerebral palsy

Cerebral palsy is the most common developmental neurological disorder, and places enormous costs on the affected individual, their family and the community. Despite the advances of modern medicine, the incidence of cerebral palsy has remained at approximately 1 in 400 children over the past 50 years. Although causation has historically been attributed to a degree of "birth asphyxia", in most cases the aetiology precedes labour and is unknown.

Major advances in genetic technology have recently identified that developmental neurological conditions such as intellectual disability, autism, epilepsy and schizophrenia are associated with pathogenic genetic mutations. The Cerebral Palsy Group is committed to identifying possible genetic causes for cerebral palsy, and in particular, to apply new generation genetic technologies to address this question.

Thanks to grants from the NHMRC, the Cerebral Palsy Foundation and the Robinson Institute, the group has established an Adelaide-based DNA biobank comprising DNA samples from cerebral palsy children



and their parents from around Australia. This unique and growing biobank is linked to detailed clinical data. In 2012, DNA from the biobank was transported to collaborating centres for genetic analysis in the USA, where it underwent exome sequencing and microarray analysis. Early data show inherited potentially pathogenic copy number genetic variations in 20% of cerebral palsy biobank cases. It is possible that such

genotypes manifest as cerebral palsy with certain epigenetic triggers. Separate multiple candidate de novo mutations were also found; their pathogenicity is currently being investigated.

Group members

Project Officer: Jessica Broadbent

Research Officers: Michael O'Callaghan, Clare van Eyk, Corinne Reynolds and Kelly Harper

PhD Candidates: Gai McMichael



Associate Professor Dominic Wilkinson

Events, illnesses and treatments in the newborn period can have profound and life-long effects. The Neonatal Medicine Group is dedicated to improving the long-term health of premature and seriously ill newborn infants, and supporting families and doctors to make appropriate and ethical decisions in the care of newborns.

Group research activities address four main themes:

- > Generating research evidence relevant and important to the care of newborn infants
- > Bringing basic science to the bedside to inform the care of critically ill newborn infants
- > Critically appraising current practice, and identifying evidence gaps for further enquiry
- > Building collaborations with research partners within the University of Adelaide, and other neonatal units in Australia and internationally

In 2012 research conducted by the Group focused on answering key questions about the safety of blood transfusion for premature newborn infants. Nutritional interventions in women and in preterm infants were also explored, with the view to reducing the burden of illness and impairment. Finally, researchers looked at approaches to improve the care of fetuses and newborn infants with life-limiting illnesses, and to provide a framework for decision-making around the threshold of viability.

Group members

Research Leaders: Michael Stark, Ross Haslam, Chad Anderson and Andrew McPhee

Postdoctoral Researcher: Vicki Xafis

ARCH Neonatal Medicine

Research evidence for the care of newborn infants

A background image showing a close-up, top-down view of a petri dish containing a yellowish-orange liquid. A glass pipette tip is positioned above the dish, with a small amount of liquid inside it. The background is a soft, out-of-focus purple and pink gradient. Several dark, circular shapes, likely the edges of other petri dishes, are visible in the corners.

Centre for Early Origins of Health and Disease

The biological predisposition towards developing many common health conditions is influenced by environmental characteristics of pre- and early postnatal life. Identification of interventions to promote 'a healthy start to life' is a key public health priority outlined by the World Health Organization and the Australian government

Directors' report

The Centre for the Early Origins of Health and Disease is a leader in the investigation of prenatal and perinatal origins of metabolic, cardiovascular, neurological, immunological and reproductive health in postnatal life.

The high regard in which the Centre is held nationally and internationally stems from its strong history and continuing focus on intergenerational health research.

Scientists, clinicians, epidemiologists, psychologists, nurses and statisticians in the Centre conduct fundamental and translational studies, ranging from molecular biology, epigenetics and physiology, to epidemiology and public health, as well as clinical medicine.

Specific research areas address:

- > How events in early life affect our health and risk of major diseases, so as to develop and test clinical and public health interventions to improve later health
- > Identification of opportunities to improve health and prevent disease among women and their children and families, focusing on both social and biological pathways at different points in the life course
- > Investigation of the neurophysiological mechanisms underlying developmental or acquired brain dysfunction, and development of novel therapies aimed at reducing the impact of these impairments on quality of life at all ages
- > Examination of how a fetus grows when pregnancy conditions for growth are suboptimal - as occurs with maternal asthma, nutritional deficiencies and impaired placental function - and the best opportunities to intervene to prevent illness and death in infants, and poor long term health

To broaden research strengths and extend outreach, Centre members at the University of Adelaide collaborate extensively with external organisations in Australia and overseas. Formal partnerships include:



- > The European Union Framework Research Collaborative Program, Early Nutrition
- > The University of Bristol MRC Unit for Integrative Epidemiology
- > The International Inflammation Network, supported by the World Universities Network Global Health Initiative

During 2012 the Centre published several key research achievements that received national and international attention due to their identification of novel pathways through which the perinatal environment impacts on lifelong health. Moving forwards, the Centre aims to expand these findings, with a view to creating solid evidence for new policy and changed clinical practice and public health policy for better health of babies, children and adults.

Professor Julie Owens, Professor Michael Davies and Associate Professor Michael Ridding,
Co-Directors

Associate Professor Vicki Clifton



Pregnancy and Development

Maternal asthma during pregnancy and managing its impacts on babies

Asthma is the most common complication experienced by Australian women during pregnancy. Strategies to improve management of maternal asthma during gestation will reduce the high risk of adverse outcomes for babies, including premature delivery, low birth weight and stillbirth. The Pregnancy and Development Group is committed to helping pregnant women and their health carers manage asthma and reduce these risks. Researchers and staff within the Group have a combined background in immunology, asthma, fetal growth, maternal and placental physiology and nutrition. Prior research has examined:

- > Aspects of the role of the immune system in contributing to worsening asthma during pregnancy
- > The role of maternal nutrition in women with asthma and its effects on fetal growth
- > Susceptibility to allergy development in children of asthmatic mothers
- > Sex-specific mechanisms of glucocorticoid resistance in the placenta and asthma management in pregnancy

More recently the group has expanded into examining health literacy and identifying ways to improve communication with pregnant women of a socially disadvantaged population. This work is funded by an ARC Linkage grant (partnered by the Lyell McEwin Hospital and conducted in collaboration with Applied Communication Collaborative Research Unit).

The Group's research activities during 2012 targeted understanding the mechanisms that worsen asthma during pregnancy, with a view to improving treatment and introducing a dedicated asthma service in the antenatal clinic. In particular, this involved the generation of nurse-led preventative health care strategies. Respiratory nurses with appropriate training can provide essential components of an asthma management service in the antenatal clinic. Group members are also examining the role of diet in improving asthma, health literacy and social media for improving communication with pregnant women and the development of new technologies for the detection of worsening asthma. A strong publication and conference presentation track record during 2012 reflected these activities.

“ The Pregnancy and Development Group is committed to helping pregnant women and their health carers manage asthma and reduce these risks ”

Group members

Emeritus Member: Basil Hetzel

Postdoctoral Fellows: Nicolette Hodyl, Annette Osei-Kumah, Michael Stark, Jessica Grieger, Astrud Tuck, Zarqa Saif and Luke Grzeskowiak

Senior Research Associate: Dianne Rodger

Research Midwife: Karen Rivers, Julia Dalton

Research Respiratory Nurse: Kate Roberts-Thomson

Emergency Department Consultant: Maureen Busuttill (also postgraduate student)

PhD Candidates: Isabella Rose-Meredith and Natalie Aboustate

Midwifery Masters Candidates: Julie Tucker and Donna Coates

Honours Students: Amy Wooldridge, Zain Ali and Nurul Zainal

Laboratory Technician: Jessica Forrest

Personal Assistant: Kelly Fulton

Affiliates: Nayana Parange (University of Adelaide), Jon Hirst and Ian Wright (The Mothers and Babies Research Centre), Karen Moritz (University of Queensland), Vanessa Murphy (John Hunter Hospital), Roger Smith (University of Newcastle) and Lisa Wood (John Hunter Hospital)

Professor Michael Davies, Professor Vivienne Moore



LIGHT

Life course and intergenerational health

It is increasingly clear that environmental factors in early life are major determinants of chronic disease risk in later life. Through this mechanism, both social and biological influences on health are transmitted from one generation to the next. The Life and Intergenerational Health (LIGHT) Group conducts research to understand the interplay of social and biological factors influencing health over the life-course, and the transmission of chronic disease risk from parents to subsequent generations. Through a series of community based studies, the Group undertakes epidemiological research to identify the causal pathways and potentially modifiable risk factors for outcomes that are of public health significance, including congenital malformations, obesity, cardiovascular disease and reproductive disorders. Members also support anthropological research to gain in-depth understanding of the social determinants of health, and undertake public health research to consider the political and gendered implications of research findings.

In 2012 the Group achieved international attention in both scientific and media circles with a New England Journal of Medicine publication showing the risk of birth defects is elevated in children conceived with infertility treatment.



While part of the risk is inherent to infertile parents, the fact that risk also varies with the type of treatment suggests that risk reduction is achievable.

In 2012 the Group also published:

- > Evidence that birth characteristics of individuals are related to their risk of developing polycystic ovary syndrome, pointing to pre-birth determinants
- > Evidence that work schedules of parents, especially family-unfriendly hours of fathers, increase the risk of child obesity
- > A critical examination of the position of women in the bio-cultural reproduction of obesity. It is concerning that women are held responsible and 'blamed' for obesity in children, without regard to their social circumstances

Group members

Deputy Director and Postdoctoral Research Fellow: Emily Steele

Research Leaders: Megan Warin and Alice Rumbold

Research Fellows: Lynne Giles, Wendy March, Malinda Steenkamp, Melissa Whitrow and Tanya Zivkovic

Study Coordinator: Kendall Smith

Statisticians: Suzanne Edwards, Chris Davies and Kristyn Willson

PhD Candidates: Renae Fernandez, Renae Kirkham, Stephanie Champion and Oana Maffei

Affiliate Members: Debbie Lawlor (University of Bristol) and David Phillips (Southampton University)



Professor Julie Owens



Early Origins

Early origins of health and disease

Obesity, diabetes, the metabolic syndrome and cardiovascular disease are amongst the most common non-communicable diseases in Australia and across the world. It is now recognised that environmental characteristics of life before birth and in infancy and childhood, predispose individuals to later develop these and other health problems. The presence of a healthy placenta that delivers appropriate nutrients and oxygen to support fetal growth is critical in this regard. The Early Origins Group conducts research to understand maternal conditions impacting on placental development, and explore how these affect supply of nutrients and other essential components to support normal growth of the fetus. Beyond the pre-natal and neonatal period, the Group is also interested in the influence of placental conditions and restricted intrauterine growth on the short and long-term health of offspring. The Group also aims to identify interventions in pregnancy or early life to 'rescue' the

growth-restricted fetus for improved survival, growth and long-term health outcomes, including risk of obesity and diabetes.

Research activities conducted during 2012 focused on collecting evidence in experimental models relating to interventions before or after birth to 'rescue' the growth-restricted fetus and improve their long term health. Outcomes were that:

- > Maternal treatment with growth hormone can improve function of the placenta, and improve fetal growth and survival
- > Neonatal treatment with a GLP-1 analogue that promotes insulin production and influences appetite control can prevent obesity onset in growth-restricted offspring

These findings suggest that therapeutic approaches to overcoming early life programming of obesity and diabetes can be achieved through targeting the growth hormone and insulin signaling pathways in the mother or her offspring.

Group members

Emeritus Professor: Jeffrey Robinson

Senior Researcher: Kathryn Gatford

Researcher: Anne Macpherson

PhD Candidates: Vincent Chu, Pat Grant, Laura Hardefeldt, Himawan Harryanto, Dane Horton, Damien Hunter, Wee-Ching Kong, Ezani Mohamed Jamil, Saidatul Naziah Mohammad and Siti Sulaiman

Research Assistant: Gary Heinemann

Affiliates: Miles DeBlasio (Cambridge University), Marie Dziadek (Garvan Institute of Medical Research), Bill Hague (Women's and Children's Hospital), Jill Lipsett (Women's and Children's Hospital), Debbie Lawlor (University of Bristol), Margaret Morris (University of New South Wales), Caroline Relton (University of Bristol), Rebecca Simmons (University of Pennsylvania), Mary Wlodek (University of Melbourne and Prema Thavaneswaran (Department of Health, SA)

Students: Sarah Cash, Hong Chu Wing, Patricia Grant, Himawan Harryanto, Damien Seth Hunter, Wee Ching Kong, Hong Liu, Saidatul Naziah Mohammad, Jamil Ezani Mohamed, Mansi Dass Singh, Siti Aishah Sulaiman, Tulika Sundernathan



Associate Professor Michael Ridding, Dr Julia Pitcher

NeuroPAD

Neuromotor plasticity and development

Development of the brain is a lifelong project. In a process known as neuroplasticity, each person's brain constantly adjusts its wiring to reflect its experiences and environmental exposures. Although neuroplasticity does occur in adults, the brain is at its most 'plastic' in fetal life and during early childhood. Unfortunately, this high degree of early life neuroplasticity means that the brains of fetuses, babies and children are highly vulnerable to developmental problems and injury. The Neuromotor Plasticity and Development (NeuroPAD) Group conducts research to determine how the functional development of the brain is altered by early life exposures (preterm birth, fetal growth restriction, maternal stress and infection) and genetic, epigenetic and postnatal environment factors. Group members also aim to translate research outcomes into interventions and treatments to improve learning, memory, cognitive and motor function in vulnerable populations, and to improve therapies for recovery from injury. In 2012 the NeuroPAD Group focused on two main complimentary activities using techniques such as non-invasive brain stimulation and electrophysiological recordings of brain and muscle responses. The first line of work examined how being born too soon or too small influences the development of the brain's cortex. In a study which received national and international attention, preterm birth – even if only a matter of a few weeks – was found to affect the cortex's ability to rewire the strength of its connections in response to brain stimulation. This data provided the first evidence of a physiological mechanism to explain why children who are born preterm (but without diagnosable brain damage) have difficulties with learning and memory. Current work is now addressing whether this outcome is associated with all types of learning, and the role of the stress hormone cortisol in its manifestation.



A second aspect of Group work during 2012 was the development and refinement of new non-invasive brain stimulation techniques for inducing functionally beneficial neuroplasticity in targeted brain regions. Investigations to explore if these techniques are also useful in reducing symptoms in conditions typified by chronic pain were also performed. These techniques may prove useful in improving motor and cognitive outcomes in preterm children.

Group members

Research Fellows:

Sebastian Doeltgen, Nicolette Hodyl

Postdoctoral Researchers:

Luke Schneider and Ann-Maree Vallence

Neonatologist: Michael Stark

Biomedical Engineer: Ruiting Yang

PhD Candidates: Mitchell Goldsworthy, Suzanne McAllister and Joanna Cole

Visiting PhD Candidate: Robin Law

Research Assistant: Ashleigh Smith

Honours Student: Kathryn Dansie

Affiliates: Angela Clow (University of Westminster), Caroline Relton (University of Bristol) and John Rothwell (University College London)

“ In a process known as neuroplasticity, each person's brain constantly adjusts its wiring to reflect its experiences and environmental exposures ”



Children's Research Centre

Childhood represents the
best opportunity to establish
good health for the rest of life

Director's report



The Children's Research Centre is the only South Australian research centre dedicated solely to child and adolescent health. The Centre has a unique capacity to link clinical expertise in childhood disease with collaborative research, and translate results into improved clinical care and health policy.

The Centre focuses on common childhood disorders including diabetes and autoimmunity, mental health, gut disorders, obesity, sleep, cystic fibrosis, infectious disease and vaccinology, allergy, rheumatology, immunology and neurodevelopment.

Whilst Centre members have a strong research focus, many are also clinicians who are dedicated to managing these childhood disorders or providing laboratory services for clinical testing. There is also a strong commitment to teaching with over 55 higher degree students in the Centre.

A core strength of the Centre is its capacity to conduct randomised controlled trials and cohort studies with collaboration between clinicians and basic scientists. Eleven national and international clinical trials relating to childhood diabetes, mental health, vaccines, allergy, and respiratory/sleep disorders were managed within the Centre during 2012.

The Centre connects the University of Adelaide and the Women's and Children's Hospital, as well as other key research institutions including the University of South Australia and SA Pathology. Members conduct international collaborations with research leaders based in other children's hospitals and universities in the UK, USA and South East Asia.

Central to the Centre's ongoing success is collaboration between clinicians, scientists and policy-makers - working together with children, their families and the community.

Professor Jenny Couper, Director

Associate Professor Simon Barry



Molecular Immunology

The molecular basis of immune tolerance and development of related therapies

One of the key questions in immunology is how a healthy immune system balances being ready to swiftly fight off pathogens, whilst maintaining tolerance to harmless challenges such as food and self tissues. A subset of immune cells known as regulatory

T cells (Tregs) is believed to play a critical role in determining such outcomes. Tregs are essential for immune tolerance, with defects in this particular cell population implicated in autoimmune disorders, cancer and other diseases. The Molecular Immunology Group conducts research to understand and characterise Tregs under normal conditions, with a view to understanding what goes wrong with these cells in immunological disorders.

The Group applies a two-pronged research approach. State of the art unbiased genome wide methods are applied in the discovery arm of the Group's program, such as searching for new biomarkers on immune cells. This includes mapping Treg gene regulation controlled by micro RNAs and FOXP3, and which genes are key for normal function. Results are then validated and translated for use as research and medical tools, using human disease cohorts where possible, including a type 1 diabetes cohort with Professor Jenny Couper (Children's Research Centre Director), to broaden clinical applicability. Using this approach, in 2012 the Group identified PI16 as a novel

human CD molecule on T cell subsets. Patents have now been filed by group members to cover applications of PI16/CD359, including isolation of human Tregs for cell therapy.

Following successful applications for funding, in 2012 the Group also commenced research addressing the roles of a protein known as FOXP3 in determining immune activity in Tregs. These projects are ongoing, and focus on:

- > The role of FOXP3 in immune tolerance and autoimmune disease
- > The role of FOXP3 in breast cancer tumour suppression

Group members

Postdoctoral Research Fellows: Timothy Sadlon and Cheryl Brown

PhD Candidates: Natasha McInnes, Steve Pederson and John Welch

Honours Students: Kelly Gembus and Kristen Malatesta

Research Assistants: Suzanne Bresatz, Grace Ang, Tzu Ying Yap and Sonia Dayan

Professor Jenny Couper



Diabetes

Prevention of Type 1 Diabetes and its complications

The incidence of Type 1 Diabetes in childhood has increased worldwide, having doubled in Australia over the last 20 years. This supports the importance of the modern changing environment in its development. If we can identify the environmental triggers we will have a way of intervening to restore a healthy immune system in the body to prevent diabetes. Children with Type 1 Diabetes have an increased lifetime risk of

heart, kidney, and eye disease due to the effect of the diabetes on their blood vessels. These first subtle changes can be detected from adolescence, when they are still at a reversible stage. Therefore prevention and intervention during childhood is very important.

The Diabetes Group conducts clinical and laboratory research which focuses on:

- > The environmental exposures that drive the development of Type 1 Diabetes
- > Immune regulatory function in Type 1 Diabetes
- > Treatment innovations to protect blood vessel health of children and adolescents, who have Type 1 Diabetes

The Group is also the Australian centre for ultrasound measurement of vascular health for the international AdDIT trial (Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial).

A national cohort study from pregnancy to determine how the modern environment drives the development of Type 1 Diabetes began in 2012. In conjunction, there were studies of immune regulatory function in preclinical and recent onset Type 1 Diabetes. The Group conducted two randomised controlled trials to assess the efficacy of metformin in preserving vascular health, and strategies to help blood glucose

control in children with cystic fibrosis. With collaborators, the group leads the South Australian arm of international trials aimed at preventing Type 1 Diabetes using immune tolerance strategies, and preventing vascular complications in adolescents. In 2012 the Group also followed a longitudinal cohort of South Australian children including healthy children, obese children and children with Type 1 Diabetes to assess the value of ultrasound for measuring blood vessel changes in early cardiovascular disease.

Group Director Jenny Couper was appointed to the steering committee of the Juvenile Research Foundation International clinical research network in Australia in 2012.

Group members

Research leaders: Alexia Pena and Simon Barry

Research coordinator: Megan Penno

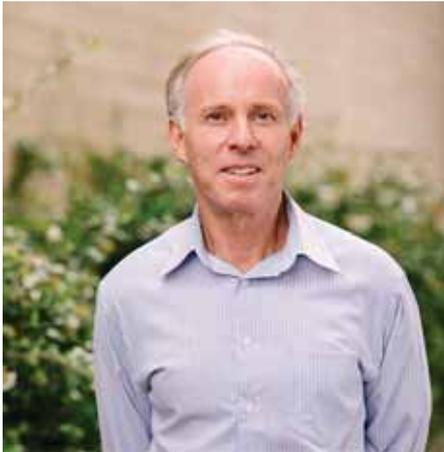
Research nurses: Sarah Beresford and Meredith Krieg

PhD candidates: Jemma Anderson (RACP Advanced Trainee), John Welch (FRACP), Shiree Perano (FRACP) and Jessica Phillips (RACP advanced trainee)

Postdoctoral research fellow: Oana Maftei

Head research sonographer: Roger Gent

Dr Michael Gold



Vaccine Safety

Detection and analysis of vaccine safety in children

At the time of licensing a new or seasonal influenza vaccine, safety information about potential rare reactions is often incomplete. Australia's current healthcare surveillance system lacks the capability to detect adverse reactions in a timely and effective manner. The goal of the Vaccine Safety Group is to address current deficiencies in surveillance by exploring health provider reporting,

active sentinel surveillance and e-Health approaches, including data linkage. Such activity is of critical importance to counter increasing public concern about vaccine safety. Without better systems to survey vaccine safety, vaccination coverage may decline and result in reduced effectiveness of immunisation programs for disease prevention.

The group achieved a strong publication record during 2012, including key results that were requested by the Commonwealth Department of Health and Ageing's Horvath Working Party of Experts for inclusion in a report responding to the Horvath Review, and the NHMRC Health & Research Ethics Working Party.

In addition, three group members completed their PhD dissertations in 2012, based on data relating to the following areas:

- > Issues around consent relating to vaccine delivery (the only Australian data on this topic)
- > Ethical and legislative barriers for safety surveillance using data linkage with the Australian Childhood Immunisation Register
- > Data on health provider and community knowledge about adverse events following immunisation

Work on developing a national vaccine safety system using data linkage is ongoing and the focus of a fourth PhD thesis.

The current research focus of the Vaccine Safety Group involves examining the feasibility and acceptability of alternate methods of vaccine safety surveillance, including data linkage and hospital-centered sentinel surveillance.

Group members

Chief Investigator and Bioethicist:

Annette Braunack-Mayer

Chief Investigator and Biostatistician: Phil Ryan

Chief Investigator: Helen Marshall

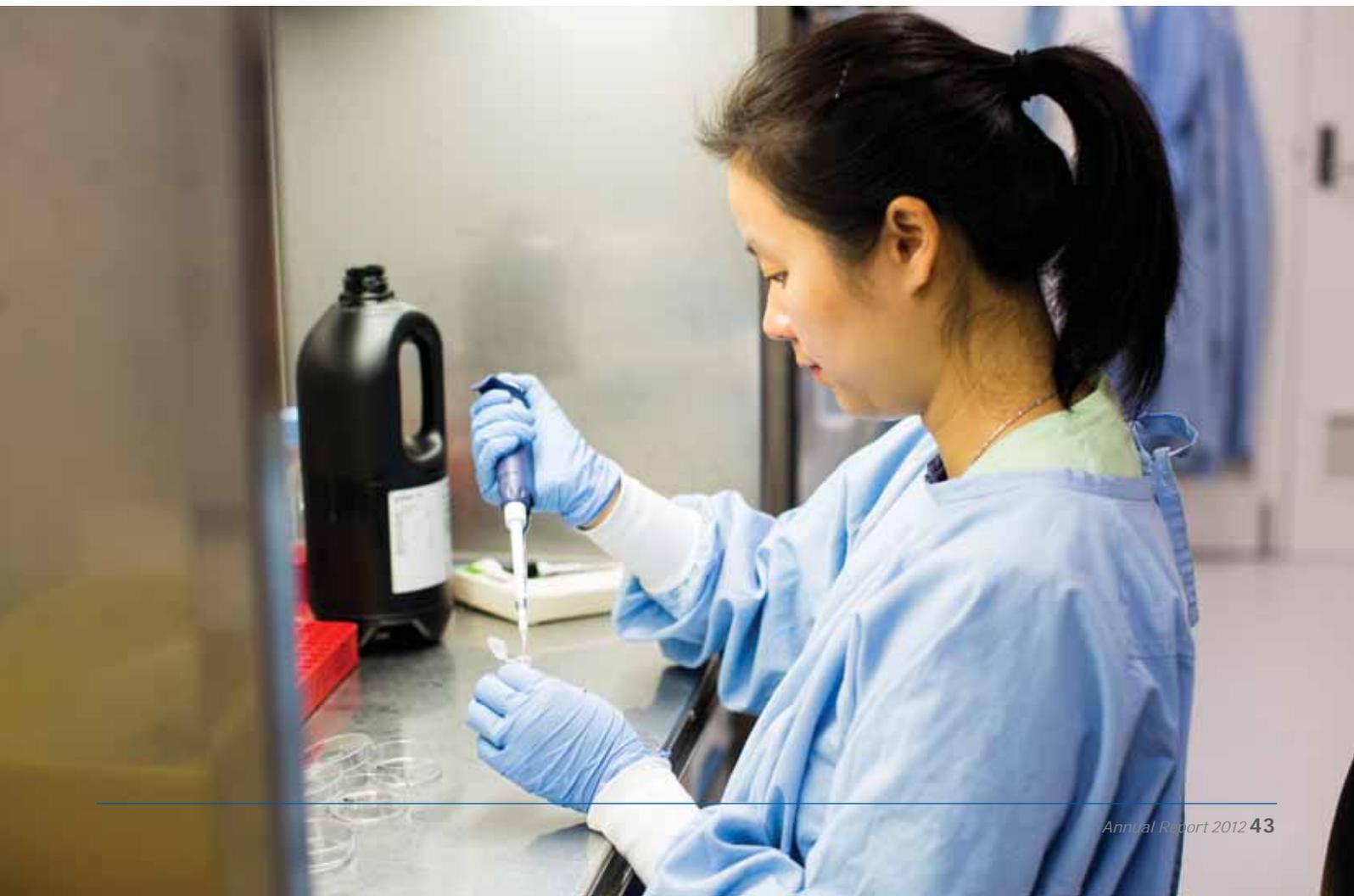
Statistician: Peter Baghurst

Research Nurse: Christine Heath and Mary Walker

Project Manager and PhD Candidate:

Katherine Duszynski

PhD Candidates: Jesia Berry, Adriana Parrella and Vicki Xafis



Professor Antonio Ferrante

Developmental Genetic Immunology

Genetic, molecular and cellular biochemistry of inflammatory diseases in children

The innate and adaptive arms of the human immune system are shaped by genetic, molecular and cellular factors before and after birth. The Developmental Genetic Immunology Group explores how these factors contribute to the development of allergic, autoimmune and infectious diseases, particularly during the prenatal and early postnatal periods. This is being achieved through studying leukocyte development and maturation, and focusing in particular on diabetes, allergy and cystic fibrosis/respiratory infections. The Group seeks to identify early immunogenetic markers that reflect susceptibility and resistance to these diseases, with a view to developing new diagnostics and treatments for patients.

The Group's major finding during 2012 related to an ongoing project that aims to tease apart the favourable (infection and cancer fighting) and unfavourable (overwhelming inflammatory) actions of the molecule Tumour Necrosis Factor, a key player in the above diseases. By constructing mutants of the receptor of Tumour Necrosis Factor, the Group scientists identified different parts of the receptor that control favourable versus unfavourable actions. This exciting and patented discovery will now be developed further with research aimed at designing new treatment options to reduce unnecessary inflammation whilst maintaining healing.

Other Group research discoveries in 2012 included:

- > Receptors for bacteria are induced in neonatal macrophages following exposure to Vitamin D/sunlight
- > Discovery of a novel mutation in the CYBB gene (coding for gp91phox protein) will improve understanding of pathogenesis in chronic granulomatous disease and



management of the condition

- > Engineering of fatty acids with insulin-like activity will assist in improving the management of women and children with diabetes
- > Characterisation of neonatal T lymphocyte development through intracellular signaling will improve risk assessment of developing allergy
- > Identified a new genetic marker for diagnosing Common Variable Immunodeficiency

Group members

Principal Scientist: Charles Hii

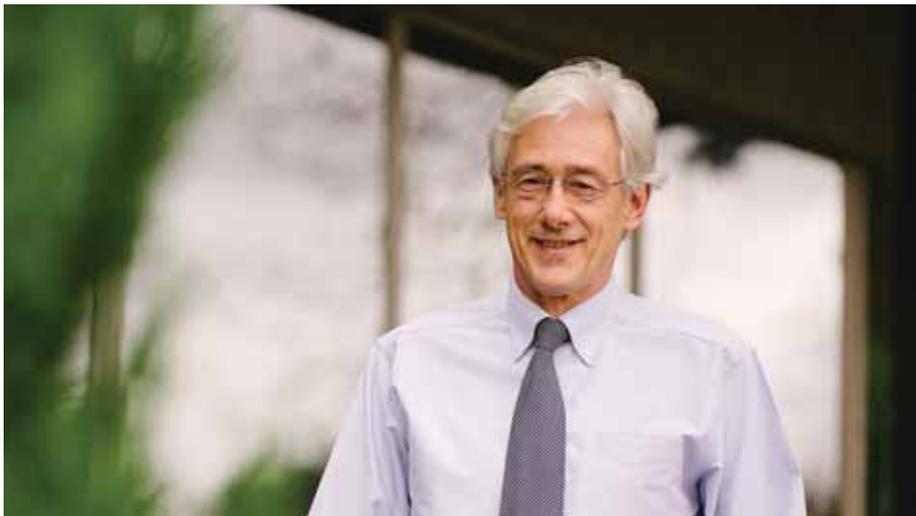
Senior Scientists: Nick Gorgani and Hameet Singh

Scientists: Bernadette Boog, Serah Harvey, Alex Quach, Nick Mabbarrack, Clare Mee and Yongqin Li

PhD Candidates: Cheung Szeyan and Usma Munawara

“ The Group seeks to identify early immunogenetic markers that reflect susceptibility and resistance to these diseases ”

Associate Professor Declan Kennedy



Sleep Disorders

Paediatric sleep disorders and their effect on children's daytime functioning and vascular health

Children spend half of their life asleep. In the past two decades it has become clear that reduced sleep quality and duration interferes with normal daytime functioning, and in particular can interfere with memory and learning.

The Sleep Disorder Group works toward two main goals:

- > To examine disruption of normal sleep architecture due to chronic childhood disorders
- > To assess the sequelae of sleep disruption on physiology and cognitive functioning in children

To date the Group has found significant decrements in daytime functioning in children with disrupted sleep due to disordered breathing, eczema or diabetes. Such children experience reductions in neurocognition and display unwelcome behavioural changes. These and other results collected over the past 15 years support the theory that sleep is indeed vital for children's learning and normal daytime functioning.

Work conducted during 2012 examined the effect of sleep fragmentation on children's vascular health. This new focus arose after review of research papers describing an elevated risk of developing vascular morbidity due to sleep deficit in adults with disordered breathing. The Group also conducted research to evaluate whether treatment of sleep disordered breathing in children has differential neurocognitive outcomes depending on the age at which the child develops the condition.

Group members

Co-directors: James Martin and Kurt Lushington

Research Leader: Yvonne Pamula

Senior Researcher: Mark Kohler



Associate Professor Helen Marshall



Vaccine Trials Unit

Vaccinology and immunology research trials unit

Immunisation remains one of the most effective public health strategies in preventing deaths and disease in children and adults. The Vaccinology and Immunology Research Trials Unit (VIRTU) at the Women's and Children's Hospital conducts clinical trials of new investigational and licensed vaccines in children, adolescents and adults in order to test their immunogenicity and safety. VIRTU also undertakes studies in infectious disease epidemiology and social epidemiology.

Data generated through these means is applied to inform public health policy and immunisation service delivery, and to ensure an evidence base for Australian immunisation programs. VIRTU is part of the National Vaccine Research Network, a collaborative group of vaccine research centres in Australia conducting national multi-centre trials and contributing to knowledge in vaccinology and development of immunisation policy.

During 2012 VIRTU performed essential research to ensure Australian children receive vaccines that are safe and effective against new and re-emerging infectious diseases. In particular, VIRTU's research program has responded to public health infectious disease priorities such as improving protection against pertussis and influenza. A new vaccine to prevent Meningococcal B strain disease has recently been recommended for licensing in the European Union. VIRTU has played a major role in clinical trial development of new Meningococcal B vaccines, and has now

“ VIRTU has played a major role in clinical trial development of new Meningococcal B vaccines ”

completed eight studies of such vaccines in adults, adolescents, children and toddlers; further studies are planned. It is hoped that a Meningococcal B vaccine will be licensed and available soon in Australia to prevent this devastating and sometimes fatal disease. Data showing the high incidence of sequelae and independent predictors of sequelae following meningococcal disease has been provided by VIRTU to the Australian Technical Advisory Group on Immunisation to support policy on the introduction of Meningococcal B vaccines.

Group members

Deputy Director: Sue Evans

Investigator: Christina Boros

Chair, Scientific Advisory Board: Geoff Davidson

Research Fellows: Suja Matthew, Trinh Tran and Nan Vasilunas

Medical Officer: Rachel Chen

Postdoctoral Fellow: Joanne Collins

Medical Scientist: Michelle Clarke

Grant-funded Scientists: Susan Lee, Jane Tidswell and Natalie Thomas

Senior Research Nurse: Chris Heath

Research Nurses: Kirsten Zyhajlo, Verity Hill, Mary Walker and Jane Tuckerman

Masters Candidate/Research Assistant: Bing Wang and Michelle Clarke

Honours Student: Nerissa Lakhan

Administrative Officer: Anne Webster

Associate Professor Taher Omari



Gastroenterology

Paediatric swallowing and motility disorders

Safe swallowing is a complex process. Disruption in swallowing function (dysphagia) and gastro-oesophageal reflux are common

in infants and young children, and can lead to very serious complications such as pneumonia, feeding failure and even early death. Dysphagia is currently most often assessed using fluoroscopy and X-ray imaging. The Gastroenterology Group develops innovative novel measurement methods for the assessment of gastrointestinal propulsive function, and is particularly focused on targeting the pathophysiology and diagnosis of dysphagia. The Group is also interested in establishing causal associations between the symptoms of reflux and other disorders that manifest similarly.

In 2012 the Group developed a new patented diagnostic tool for the analysis of pressure and flow measurements taken during swallowing, and established proof of concept that this method can assess swallowing function and aspiration risk without need for X-rays. Current work is generating the evidence-base needed to underpin the translation of this invention from a research tool into one suitable for routine clinical practice. The method should

be available for routine use by doctors worldwide within the next 2-3 years.

The Group also completed research activities in two NHMRC-funded clinical trials during 2012:

- > Investigation of upper gastrointestinal propulsive dysfunction secondary to allergic inflammation in infants with cow's milk protein allergy
- > Investigation of a new non-radiological technique to screen dysphagic children for risk factors that are associated with swallowing problems and aspiration

Group members

Emeritus Professor: Geoffrey Davidson

Research Associate: Stamatiki Kritas

Research Associate: Rammy Abu-Assi

Research Nurse: Lisa McCall

Speech Pathologist: Lara Ferris

Biomedical Engineer: Malcolm Bakewell

Professor Michael Sawyer



Research Evaluation

Evaluating the effectiveness of interventions designed to support mothers and infants

Optimal physical and mental health in women and their children is critical to develop strong and resilient communities. Staff in the Research and Evaluation Unit, based in the Women's and Children's Health Network, are working in partnership with the Child and Family Health Service (CaFHS) in South Australia to improve the health and wellbeing of mothers and children.

During 2012, the Group completed an evaluation of the effectiveness of the South Australian Nurse Family Home Visiting Program

(SA-FHV) in improving the wellbeing of mothers and infants during a child's first two years of life. The impact of the SA-FHV program on maternal mental health, parenting quality, and the social, emotional and language development of infants among different family groups (e.g. single-parents versus two-parent families) was assessed. Once data analysis is completed, the knowledge gained from this research will improve identification of family groups who benefit most from the SA-FHV program, and provide information to improve the program's effectiveness in other family situations.

The Group also initiated a unique web-based support program for new mothers during

2012: Mum's etalk (www.mumsetalk.com.au). This program combines the face-to-face skills of CaFHS nurses with internet-based technology to:

- > Provide mothers with accurate information about infants and their care
- > Offer mothers the opportunity and capacity to confidently connect with other parents via online parent groups through the website
- > Create an online community of parents for the safe sharing of information and practical ideas about parenting

This resource is currently under further development and evaluation.

Group member Richard Spod (along with the Centre for Education and Training Digital Media Unit, Women's and Children's Health Network) received the SA Health 2012 Minister's Innovation Award for his work in community health.

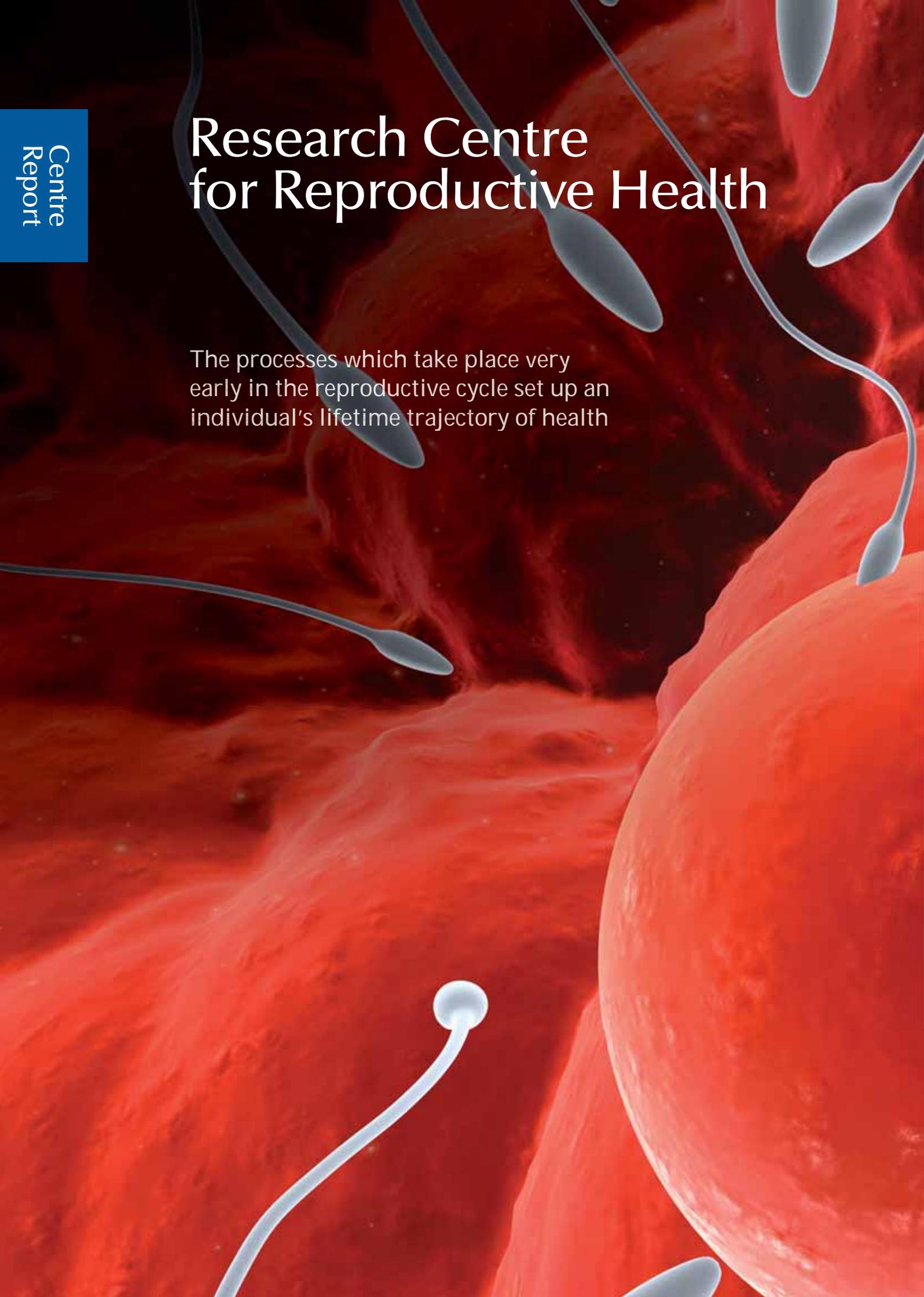
Group members

Postdoctoral Research Scientist: Lauren Miller-Lewis

Senior Project Officer: Jenny Clark

PhD Candidates: Sara Pfeiffer, Amy Kaim

Research Assistants: Richard Spod, Linda Frost and Olivia Carger

The background of the entire page is a microscopic illustration of sperm cells. The sperm are depicted as small, light blue, tadpole-like structures with long, thin tails. They are swimming in a thick, red, textured fluid that resembles biological tissue or a fluid medium. The lighting is dramatic, with highlights on the heads and tails of the sperm, creating a sense of movement and depth. The overall color palette is dominated by reds and oranges, with the light blue of the sperm providing a strong contrast.

Research Centre for Reproductive Health

The processes which take place very early in the reproductive cycle set up an individual's lifetime trajectory of health

Directors' report

A better understanding of germ cell biology, embryo development and the events of establishing pregnancy have significant public health impact by informing the reproductive choices of women and men and the health of their children from before birth to adulthood.

The Research Centre for Reproductive Health (RCRH) is a world leader in reproductive health research, innovation and discovery. Working at the interface of biomedical science and clinical medicine, Centre members explore the fundamental biology of reproduction and translate scientific discoveries into practical health and industry outcomes which benefit Australian and international communities.

The Centre is strongly founded in an ethos of working collaboratively to integrate core strengths across the continuum of reproductive physiology. Employing advanced genetic and bioinformatic technologies, RCRH researchers are addressing important gaps in basic cellular and molecular knowledge and applying this clinically to optimise the critical early stages of life spanning from pre-conception to birth. Shared state-of-the-art Centre facilities offer members the opportunity to combine expertise in cell biology,

immunology, endocrinology, obstetrics and gynaecology and cancer biology to investigate key research questions spanning the following areas:

- > Ovarian and Follicular Function
- > Oocyte and Early Embryo Development
- > Uterine Biology
- > Embryo Implantation and Placental Development
- > Male Reproduction
- > Reproductive Immunology
- > Reproductive Biotechnology
- > Nutrition, Environment and Reproduction
- > Early Life Programming of Fetal Development and Adult Health
- > Menopause
- > Infectious Diseases of the Reproductive and Gestational Tissues
- > Cancers of the Reproductive System
- > Breast Biology and Cancer

Centre members are based at the North Terrace and Roseworthy campuses of the University of Adelaide as well as The Queen Elizabeth Hospital, the Royal Adelaide Hospital, the Lyell McEwin Hospital and the Women's and Children's Hospital.

The Centre also engages in numerous active and ongoing international collaborations, a reflection of the high regard it holds with scientists across Europe, the UK, North America and Asia.



The Research Centre for Reproductive Health is recognised as a world-class hub for basic and applied biological research. Moving forward, we aspire to build on our strong track record of discovery research and translating key scientific findings into evidence-based advice for couples planning pregnancy, and new treatment options for infertility, miscarriage and pregnancy disorders.

Professor Sarah Robertson and Associate Professor Darryl Russell, Co-Directors

Professor Bill Breed

Comparative Reproductive Biology

Comparative and evolutionary studies of mammalian reproduction

Understanding and manipulating mammalian reproduction is dependent on in-depth knowledge of the anatomy, cell biology, and evolution of reproductive tissues and processes. The Comparative Reproductive Biology Group studies morphological diversity and evolution of mammalian gonads, gametes, and their interaction at fertilisation.

Specific research goals are to:

- > Determine the selective evolutionary pressures that have resulted in the interspecific diversity in form of mammalian testes, sperm, female reproductive tissues, eggs and egg coats
- > Identify the molecules involved in sperm - egg interaction at the time of fertilisation in both marsupial and eutherian mammals
- > Describe co-evolution of cellular processes of sperm - egg interaction at the time of fertilisation
- > Determine the environmental control of reproduction of mammals occurring in extreme environments

By focusing on these areas, the Group hopes to develop practical applications such as improving breeding programs for threatened species and designing immunocontraceptive strategies to control pest animals.

In 2012 the Group completed studies on comparative morphology of male and female reproductive tracts. Results showed:

- > Co-evolution in morphology of the distal region of the male and female reproductive tracts
- > Species with very small testes produce highly polymorphic sperm populations in which cryptic female choice occurs for particular sperm phenotypes

Building on these results, a study on the evolution of the gametes themselves has now commenced together with an investigation on the environmental control of reproduction. Early evidence suggests co-evolution of sperm design in males with the structure of the egg coat, the zona pellucida, in females.

The group has several international collaborations including with Syracuse University, New York, University of California - Davis, University of Glasgow, the National Museum, Bloemfontein and the University of Western Cape, South Africa.



Group members:

PhD Candidates: Liberty Olds, Katherine Speight, Karleah Trengove and Harsha Wechalekar

Honours Students: Yun Wang and Katherine Ferres

Research Assistant: Chris Leigh

Dr Rob Gilchrist



Oocyte Biology

Molecular determinants of oocyte biology

Oocyte development is a dynamic process that relies on the interaction of germ cells with somatic cells in their environment, particularly the neighbouring cumulus cells. The Oocyte Biology Group conducts basic

discovery research on oocyte-somatic cell interactions as a determinant of subsequent embryonic development. Specific activities focus on defining oocyte-cumulus cell interactions, oocyte GDF9 and BMP15 paracrine signalling and regulation of oocyte meiosis, as well as developing oocyte in vitro maturation systems for novel reproductive technologies including drug-free strategies for human in vitro fertilisation (IVF).

Experimental work conducted during 2012 focused strongly on oocyte-secreted GDF9 and BMP15 biology, including research to:

- > Elucidate the mechanism by which the oocyte-secreted growth factors GDF9 and BMP15 interact to yield potent synergistic effects on ovarian somatic cells
- > Understand actions and differences in species-specific aspects of these proteins. This work was conducted in a collaborative research project lead by collaborators at Prince Henry's Institute (Clayton, Victoria)
- > Determine the effect of forms and doses of proteins on oocyte quality and developmental potential during in vitro maturation

Additional research addressed how cAMP regulates oocyte-cumulus cell interactions and thereby improves oocyte quality and developmental potential during in vitro maturation. Finally, Group members looked into the impact of age on ovarian function, investigating somatic cell contributions to oocyte and ovarian ageing.

During 2012 the Oocyte Biology Group continued to cement its strong collaborative relationship with research groups in mainland China, visiting six clinical units in the country thanks to support from the Cook Adelaide Medical Fellowship.

Group members

Research Officer and Laboratory Manager: Lesley Ritter

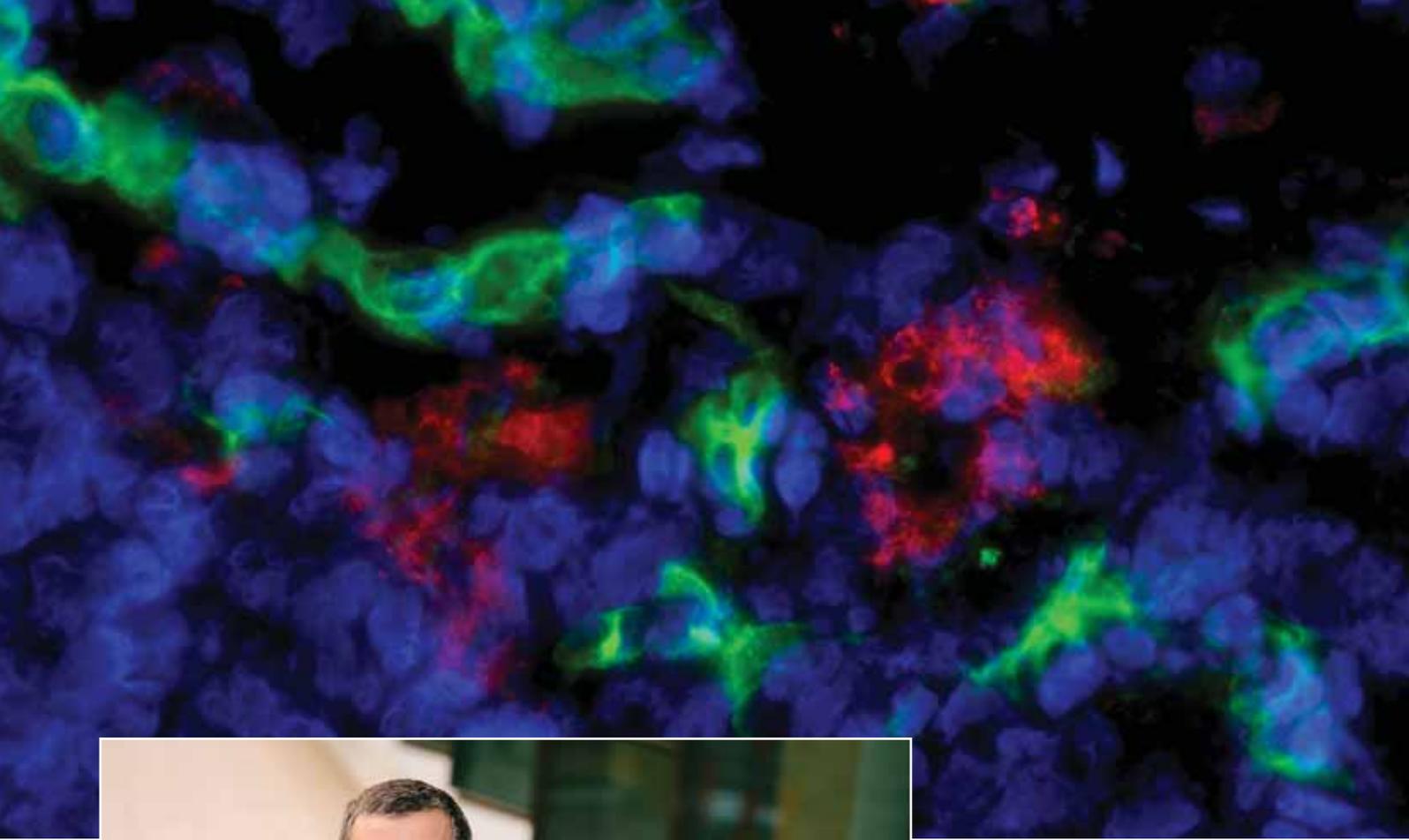
Visiting Senior Scientists: Haitao Zeng and Satoshi Sugimura

Visiting Scientist: Ren Zi

PhD Candidates: Dulama Richani, Jaqueline Sudiman and Ryan Rose

Honours Student: Melissa White

Research Assistant: Xiaoqian Wang



Dr Frank Grutzner

“ The Group seeks to identify early immunogenetic markers that reflect susceptibility and resistance to these diseases ”

Group members

Visiting Research Fellow: Dan Kortschak

Lecturer: Tasman Daish

PhD Candidates: Aaron Casey, David Stevens, Deborah Fernanda Toldo-Flores, Megan Wright, Chuan He and Reuben Jacob

Mammalian Reproduction

Molecular basis of mammalian reproduction and metabolic control

The Mammalian Reproduction Research Group uses a comparative approach to investigate the evolution and relevance for human disease of key genes involved in mammalian reproduction and metabolic control. The Group studies gene evolution in mammalian species distantly related to humans – monotremes in particular. Monotremes (platypus and echidna) have an extraordinary sex chromosome system that can reveal novel genes and pathways involved in sex determination and differentiation in all mammals, including humans. Monotremes have also undergone radical changes to their stomach anatomy and physiology, accompanied by massive loss of genes involved in digestion. As a

result, studying monotremes provides the opportunity to identify the role of key genes involved in stomach function and metabolism in humans and other mammals. Such research may lead to the identification of new therapeutic targets for metabolic diseases such as diabetes.

During 2012, the Group discovered that genes involved in a non-protein coding RNA pathway are expressed in the mammalian ovary and in human ovarian cancer. Current research activities are aimed at better understanding the role of this pathway in ovarian function, in ovulation and in the origin and progression of ovarian cancer. The group also applied a combination of genetic and biochemical approaches to investigate the function of platypus genes in metabolic control, focusing in particular on insulin release in the pancreas.

Associate Professor Leonie Heilbronn, Professor Robert Norman

Metabolism and Health

Metabolic consequences of ovarian stimulation and in vitro fertilisation

The number of children and adults conceived by in vitro fertilisation (IVF) now totals more than five million across the world. Increasing evidence suggests that IVF children have altered health profiles as compared to their non-IVF peers, including increased fatness, raised blood pressure, increased fasting blood glucose and triglycerides and lower flow mediated blood vessel dilation. The risk that IVF-induced changes in metabolic processes persist to adulthood is supported by published reports in the scientific literature. These papers show that adult mice conceived by IVF show increased body fat and fasting insulin, increased systolic blood pressure, and impaired glucose tolerance. The Metabolism and Health Group aims to provide new data regarding long-term health consequences of IVF, and drive further research into best practice of IVF.

Group studies conducted during 2012 focused on measuring metabolic health indicators in adult humans conceived by IVF. This group was found to have significantly lower insulin sensitivity by clamp as compared to age and body mass index



matched control adults conceived naturally. Such changes may be associated with increased risk of type-2 diabetes later in life. However, human studies cannot determine whether these differences are due to the IVF procedure itself or are a result of genetics, socio-economic status, or parenting differences between these groups. Focusing on the medical arm of this problem, the Group is now directing research efforts on mouse studies. In particular, the Group



aims to determine if metabolic changes are associated with the process of controlled ovarian hyperstimulation used to collect eggs for IVF, and/or in vitro culture of embryos.

Group members

Postdoctoral Researcher: Rachel Wood

Clinical Research Coordinator: Helen Alvino

PhD Candidates: Miaoxin Chen and Thomas Butler

Research Assistants: Briohny Bartlett

Professor Stefan Hiendleder



Epigenetics and Genetics

Epigenetics and genetics in pre- and postnatal development and health

Birth weight is strongly associated with developmental capacity and the achievement of positive health outcomes throughout life. It is now clear that weight at birth is determined not only by genes, but also epigenetic factors such as imprinting that regulate gene expression and phenotype. The Epigenetics and Genetics Group focuses on understanding how prenatal epigenetic mechanisms and programming affect birth weight.

The Group has developed a world-wide unique bovine resource collection to quantify differences in epigenetic modifications and mechanisms, and measure their impact on embryonic, fetal and postnatal growth and development. The bovine model is suitable to address fundamental questions in human reproductive biology due to similarities in gene structure, developmental biology and reproductive performance between the two species. Epigenetic effects of in vitro fertilisation procedures and of somatic cell nuclear transfer in stem cell production are also assessed in the bovine model.

Using this model system, The Group conducted research in two main areas during 2012:

- > Identification of imprinting for three genes in human and bovine placenta, results which were published in PLoS ONE. Contrary to previous assumptions, this study also identified that in vitro embryo culture did not change imprinting in the bovine model
- > Effects of maternal and paternal genomes on fetal muscle development, and how imprinting of maternally expressed H19 affects muscle mass

Group members

Postdoctoral Research Assistant: Dana Thomsen

PhD Candidates: Consuelo Amor Estrella, Mani Ghanipoor-Samami, Ali Javadmanesh and Ruidong Xiang



Dr Louise Hull



“ The Endometriosis Group aims to improve the understanding of the pathophysiology of endometriosis in order to develop better diagnostic and therapeutic tools for this disease ”

Endometriosis

Pathophysiology of endometriosis and development of clinical tools

Endometriosis is a condition experienced by 6-10% of reproductive age women, and occurs when the lining of the uterus grows at abnormal sites in the pelvis. Affected women endure debilitating pain with menstruation, and experience problems with fertility. Surgery is the only method currently available to accurately diagnose endometriosis, and those found to be positive often endure repetitive and chronic regimens to treat the condition. The Endometriosis Group aims to improve the understanding of the pathophysiology of endometriosis in order to develop better diagnostic and therapeutic tools for this disease. To meet their research goals, the Group utilises several in vivo mouse models in combination with sophisticated molecular and cellular laboratory techniques.

Prior research from the Group established that small genetic markers (microRNAs) are implicated in the pathogenesis of

endometriosis and appear to interact with gene polymorphisms to influence disease susceptibility. In 2012 commercial funding was obtained from Bioinnovation SA to develop a plasma microRNA based diagnostic test for endometriosis. Research activities towards this goal are ongoing. A provisional patent for plasma microRNAs as a diagnostic tool for endometriosis has been filed.

During 2012 the Group also began studies evaluating the role of microRNAs in human endometrial tissues, with results explored further in animal models. A third stream of research explored the dynamics of immune cells in endometriosis, and the role of microRNAs in regulating this activity.

Group members

Senior Postdoctoral Scientist: Jonathan McGuane

Postdoctoral Scientist: Zhao Wang

PhD Candidates: Zahied Johan and Vicki Nisenblat

Honours Student: Katherine Watson

Summer Student: Gabriel Kuo

Associate Professor Wendy Ingman

Breast biology and Cancer

Mammary gland biology in health and disease

The breast is one of the most prominent secondary sexual characteristics in women, and yet scientists still understand little about how this tissue functions in health and disease. Breast cancer is the most prevalent cancer type among women, with over 13,000 new cases diagnosed each year in Australia and the incidence of this deadly disease is rising. Another breast disease, mastitis, is a common and poorly understood inflammatory condition that plagues women during lactation, causing pain, fever, low milk supply and early cessation of breastfeeding.

The Breast Biology and Cancer group aims to:

- > Understand why the breast has such high susceptibility to cancer and the biological mechanisms that increase a women's risk of developing the disease
- > Work towards developing novel therapies that reduce breast cancer risk
- > Examine the cellular mechanisms that lead to breast inflammation in mastitis
- > Investigate potential therapies to quickly and effectively prevent the symptoms of mastitis

In 2012 the Group made considerable progress in setting up a unique bank of

human breast tissue, primary breast cells and blood samples matched with detailed clinical information regarding breast cancer risk. This bank will allow mapping of the immune cell characteristics of human breast tissue with disease outcomes, and compliment previous findings addressing how the immune system functions in the mouse mammary gland. The Group also worked in animal disease models to explore new roles for genes associated with increased breast cancer risk. A novel biological pathway that affects mastitis disease severity was also identified, opening up exciting possibilities for innovative therapeutics.

The Group was also proud to collaborate with South Australian Breast Cancer Study Group and Dr Theresa Hickey (University of Adelaide) to create the South Australian Breast Cancer Showcase 2012. The Showcase brought together researchers, clinicians and breast cancer survivors to discuss issues in breast cancer research and work towards a breast cancer-free future.

Group members

Postdoctoral Researchers: Pallave Dasari, Danielle Glynn and Mark DeNichilo

Research Officer: Leigh Hodson

PhD Candidates: Siti Mariam Noordin and Sally (Xuan) Sun

Research Nurse: Kathy Mildren



“Breast cancer is the most prevalent cancer type among women, with over 13,000 new cases diagnosed each year in Australia”

Professor David Kennaway



Circadian Physiology

Disruption of circadian rhythms and altered metabolism

Many biological processes operate under circadian periodicity, with a cycle of

approximately 24 hours. More than 1.4 million Australian shift-workers experience disrupted circadian hormonal and sleep rhythms, irregular eating patterns and insufficient exposure to daylight. Although studies have shown these people to be at an increased risk of developing chronic diseases, the mechanisms underlying this process are yet to be identified. The Circadian Physiology Group investigates genetic and related mechanisms underlying altered glucose metabolism resulting from disruption of circadian rhythms. Using animal models, research focuses on two main areas:

- > Circadian control of metabolism in adult males
- > Impact of simulated shiftwork during pregnancy on metabolic function in offspring

During 2012 the Group completed studies describing the effects of the loss of function of a key clock gene (*Bmal1*) in mice on adipose tissue function. Results

demonstrated that arrhythmic mice are obese and demonstrate aberrant patterns of adipokine secretion. These results are consistent with the increased risk of developing obesity observed in human shift-workers. In addition, ongoing research on the effects of shiftwork simulation in pregnant rats identified several changes, including:

- > Disruption in the timing of food consumption and downstream metabolic processes
- > Reduced maternal weight gain
- > Programming of poor metabolic homeostasis in the offspring

Group members

Research Fellows: Michael Boden and Tamara Varcoe

Research Officers: Leewen Rattanaraty, Mark Salkeld and Athena Voultisios

Dr Michelle Lane



Gamete and Embryo Biology

Molecular mechanisms of environmental impacts on biology of gametes and embryos

It is clear that parental exposures to environmental factors alter the health of progeny. One of the mechanisms through which this occurs is maternal and paternal programming, whereby environmental cues create changes in gametes – eggs and sperm – which are then passed on to embryos at fertilisation. The Gamete and

Embryo Biology Group conducts research to investigate the molecular changes that occur to gametes and which might be responsible for this non-genetic transmission. Examples of potential molecular mediators of heritable non-genetic molecular alterations include mitochondrial dynamics, DNA methylation, DNA damage, chromatin structure and packaging, microRNAs and histone/protamine modifications.

The Group is also interested in identifying possible interventions related to these changes.

In 2012 the Gamete and Embryo Biology Group published the first evidence that paternal obesity can induce a sub-fertility phenotype in two generations of offspring in mice. The Group also published a report that obesity-induced impairment in rodent sperm parameters can be restored by a diet/exercise intervention. Additional research activities focused on:

- > Determining the mechanisms of paternal obesity programming of sub-fertility in offspring
- > Further delineating the role of diet/exercise interventions in reversing obesity-induced perturbations in sperm
- > Determination of the impact of embryo culture on efficiency of embryonic stem cells
- > Assessment of the ovarian follicular environment in women with diminishing ovarian reserve

Group members

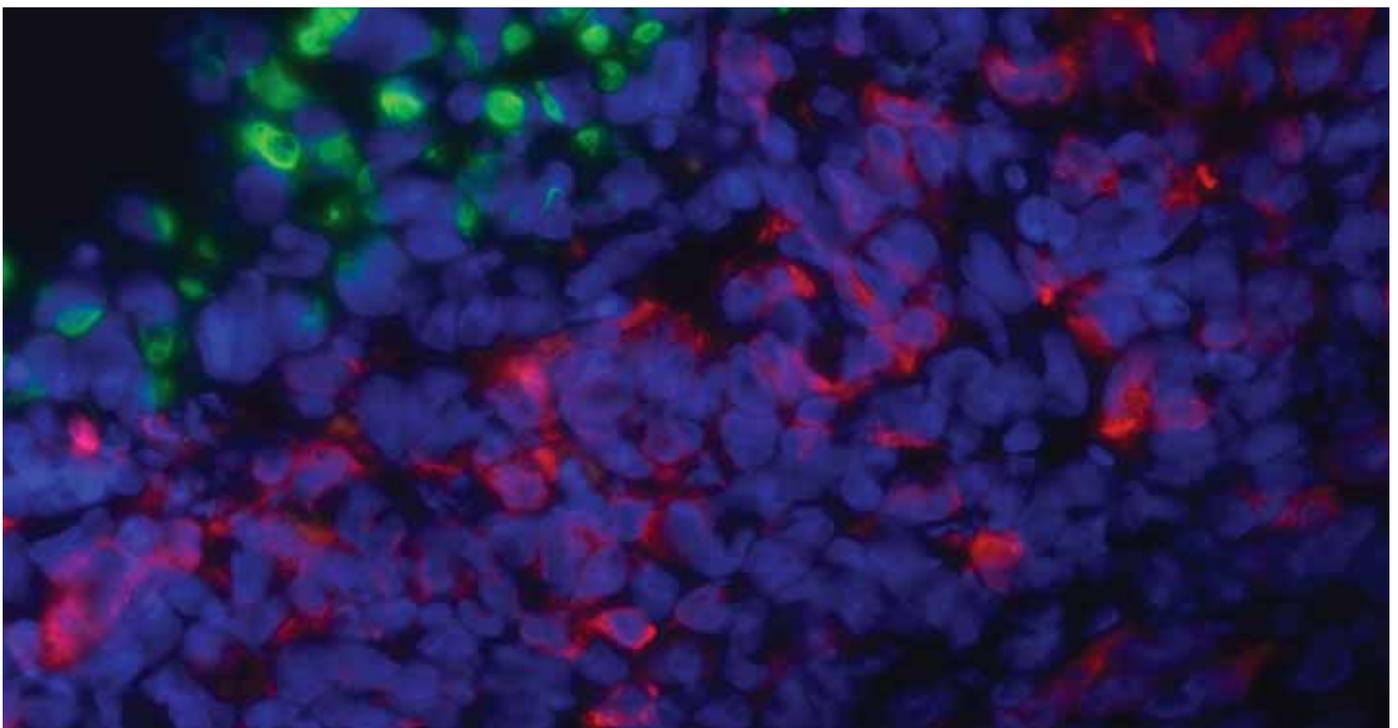
Research fellow: Tod Fullston

Postdoctoral researchers: Maria Ohlsson Teague

PhD candidates: Leanne Pacella, Nicole Palmer and Jared Campbell

Honours students: Marni Spillane, Suzanne Good and Helana Shehadeh

Research assistants: Verity Bell, Lauren Sandeman and Wan Xian Kang



Associate Professor Martin Oehler, Dr Carmela Ricciardelli

Reproductive Cancer

Identification of novel biomarkers and therapeutic targets for ovarian cancer

Ovarian cancer is the leading cause of death from gynaecological malignancies, affecting approximately 1 in 90 women in Australia. Over 70% of affected patients present with advanced disease. Despite improvements in surgical and chemotherapeutic treatment options, ovarian cancer mortality rates have not changed dramatically over the last decade. Improving ovarian cancer survival will require the development of novel ovarian cancer biomarkers for early detection and more effective targeted molecular therapeutics. The Reproductive Cancer Group is focused on conducting research to improve understanding of the mechanisms of ovarian cancer spread, resistance to chemotherapy and the identification of novel biomarkers for its detection.

Previous studies identified the protein annexin A2 to be up-regulated in the conditioned media of co-cultured ovarian cancer and peritoneal cells, suggesting it may play a role in disease progression. New work conducted in 2012 found annexin A2 to be highly expressed in up to 90% of serious ovarian cancers. Suppression of annexin A2 production was found to block key in vitro indicators of ovarian cancer metastatic capacity, such as cancer cell motility, peritoneal cell adhesion, and invasion. Subsequently, in vivo models were developed to assess the role of annexin A2



in cancer invasion and metastasis. These models included the chick chorioallantoic membrane assay and a non-invasive whole-body bioluminescent imaging xenograft mouse model. Overall, the Group's 2012 research activities suggest that annexin A2 may play a critical role in ovarian cancer metastasis. Further work will address whether this molecule may be a new therapeutic target for treating ovarian cancer. This work was funded by Cancer Council SA and the South Australian Health and Medical Research Institute (SAHMRI).

Group members

Research Officer: Alison Elder

PhD Candidates: Noor Lokman

Research Assistants: Carmen Pyragius and Anita Oehler



“ New work conducted in 2012 found annexin A2 to be highly expressed in up to 90% of serious ovarian cancers ”

Professor Claire Roberts, Professor Gus Dekker



Placental Development

Placental development and maternal adaptation to pregnancy

More than one quarter of pregnancies in Australian women are associated with pathologies of the placenta which result in miscarriage, preeclampsia, intrauterine growth restriction, preterm birth, unexplained stillbirth and placental abruption. These conditions are believed to stem from impaired placental invasion and inadequate physiological transformation of the uterine spiral arteries to ensure appropriate maternal blood supply to the placenta. There are currently no clinical assessments available to determine which women are at risk of these conditions. As a result, adverse pregnancy outcomes due to placental pathologies often cannot be prevented. This is particularly an issue for first pregnancies, where no prior history can be used to predict poor outcomes.

The Placental Development Group conducts cellular and molecular research to elucidate mechanisms that govern normal and abnormal placental development. Projects conducted during 2012 included:

- > Identification of single nucleotide polymorphisms in mother, father, baby trios in prediction of pregnancy complications
- > The role of vitamin D in placentation, using human and mouse studies
- > The role of hypoxia in early placental differentiation
- > Sex differences in the human placental transcriptome



The Group also has a strong focus on identifying genetic, nutritional, lifestyle and clinical factors that associate with pregnancy outcome. These studies are ongoing, and conducted in collaboration with other Robinson Institute research groups through well-described pregnancy cohorts. In 2012 the Group published a high impact study that identified several risk factors for preterm birth, including smoking of marijuana during pregnancy. Other publications this year identified genetic variants and clinical and lifestyle factors that associate with pregnancy complications.

Overall, research conducted by this Group is contributing to a better understanding of how placental complications develop, and is identifying factors that place women at risk. Some of these factors may be amenable to intervention in the future.

Group members

Postdoctoral Research Fellow: Denise Furness

NHMRC Australian Biomedical Training Fellow: Amanda Highet

W Bruce Hall Cancer Council Research Fellow: Tina Bianco-Miotto

PhD Candidates: Prabha Andraweera, Sam Buckberry, Jessica Laurence, Shalem Yiner Lee, Catherine Dee McCormack, Ang Zhou and Sultana Khoda

Research Assistant: Dylan McCullough



Dr Rebecca Robker



Ovarian Cell Biology

Cellular mechanisms driving ovarian function

Ovary and oocyte biology is at the core of many aspects of women's health. To prevent pregnancy and control problems associated with the ovulatory cycle, a high proportion of adolescents and women use the hormonal 'pill' to prevent ovulation. Conversely, when women do want to conceive a child, inability to ovulate is one of the most prevalent causes of female infertility. Obesity further complicates the biology of ovulation and pregnancy, especially in Australia where obesity rates are amongst the highest in the world. Obesity is associated with reduced female fertility, altered embryo growth and elevated risk of obesity in offspring. Such

changes are thought to stem primarily from metabolic disruption of oocytes, although the exact mechanisms by which this occurs remain unknown. Unraveling the cellular and molecular details of ovarian function is critical to provide data for evidence-based health policies and pre-conception advice for women.

The Ovarian Cell Biology Group works towards two broad aims:

- > Discover how the cells within the ovary provide nutritional information to the oocyte and then trigger its timely release into the oviduct
- > Identify and investigate genes that are essential for ovulation, and work towards discovering novel targets for potential anovulation therapies and non-steroidal contraceptives

In 2012 the Group uncovered new details of how oocyte release occurs in the normal ovary. Results demonstrated that the cumulus cells surrounding the oocyte adopt invasive capacities, similar to metastatic cancers, which may enable them to penetrate the ovarian wall and release the oocyte. The Group also identified genes that are controlled by the hormone progesterone, which is essential for ovulation. Current research is targeted at identifying the roles of these genes in guiding the oocyte complex as well as sustaining the embryo in the oviduct.

Group research also focused on the impact of obesity on oocyte function. Studies conducted with obese women showed that fluid surrounding the oocyte contains increased levels of harmful fat. Experiments in mice showed that oocytes exposed to high levels of lipid undergo a lipotoxicity stress response, reflected as damage to their mitochondria and often cell death. This response was able to be 'rescued' by treatment with a class of compounds that is now under further investigation as a potential agent to improve fertility in humans and agricultural species such as cattle. A patent application submitted by the Group in 2012 describes the discovery of these compounds.

Group members

Clinical Researcher: Robert Norman

Postdoctoral Researcher: Linda Wu

Visiting Scientist: Yan Meng

PhD Candidates: Lisa Akison, Astrud Tuck and Victor Miao Xin Chen

Honours Students: Marie Anastasi and Siew Wong

Masters Student: Tawiwan Pantasri

Research Assistant: Jamie Voueleng Zhang

Professor Sarah Robertson



Reproductive Immunology

Immune cells and cytokines in fertility and pregnancy health

The female reproductive tract has the distinct challenge of nurturing the oocytes, embryo and fetus to ensure healthy reproduction. These cells and tissues are essentially 'foreign' and thus the immune system is intimately involved in their survival and development to ensure optimal pregnancy outcome. The Reproductive Immunology Group conducts research to define how immune cells and their regulating cytokines contribute to the events of embryo development and implantation, placental development, fetal growth and ultimately birth. Group members

also investigate the important contribution of male seminal fluid in female reproductive tract function. This research reveals new insights into our fundamental biology and offers clues to understanding the immune origins of disorders including infertility, miscarriage, preeclampsia and preterm birth, thereby informing new treatment strategies for these conditions.

In 2012, Robertson's team published the first demonstration of the cervical immune response to seminal fluid exposure after coitus in women (in collaboration with Dr Kristina Gemzell-Danielsson, Karolinska Institute, Sweden). Key questions regarding the role of seminal fluid in initiating immune changes in the female reproductive tract have also been addressed. These changes include the generation of regulatory T cells that mediate immune tolerance in the endometrium to allow the embryo to implant and form a firm placental attachment. They have shown for the first time that sperm, as well as seminal plasma, can interact with female tract epithelial cells to induce a complex gene expression and microRNA response, which in turn influences female immune adaptation for pregnancy.

Additional projects in 2012 focused on:

- > Investigating how inflammatory perturbation in the periconceptual period influences reproductive success and offspring health

- > Defining the role of pro-angiogenic macrophages in development of the corpus luteum and progesterone production in early pregnancy
- > Understanding pathways by which maternal immune and inflammatory parameters impact the timing of birth and incidence of preterm delivery

Excitingly, 2012 also saw the launch of EmbryoGen into the American market after receiving approval from the US Food and Drug Administration. EmbryoGen is a GM-CSF-containing treatment product for miscarriage, and was developed in collaboration with Origio A/S (Denmark) based on Dr Robertson's prior research findings.

Group members

NHMRC Australian Biomedical Training fellow: Kerrilyn Diener

Senior Postdoctoral Researcher: David Sharkey

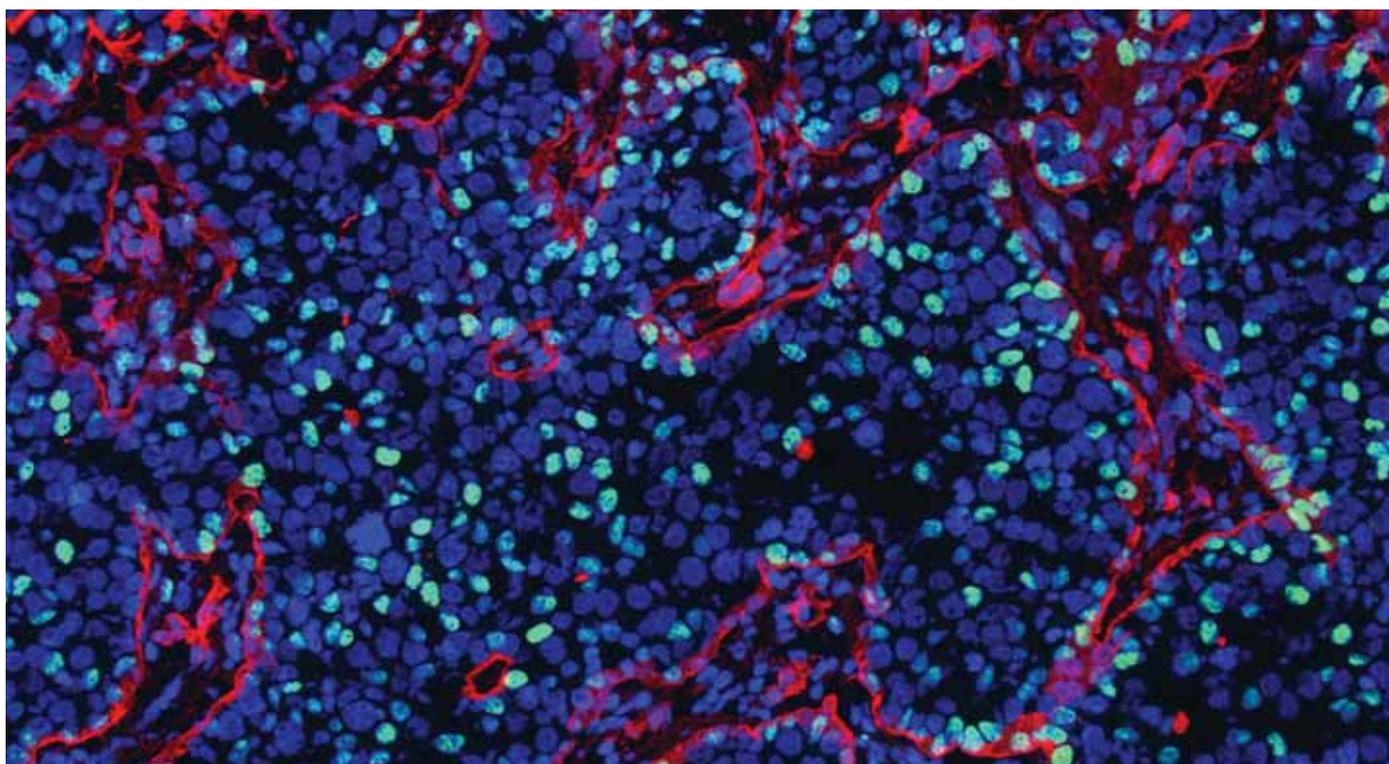
Postdoctoral Researchers: John Schjenken, Alison Care and Nardhy Gomez-Lopez

Visiting Scientist: Sabine Segerer

Research Officer: Camilla Dorian

PhD Candidates: Peck Yin Chin and Jelmer Prins

Honours Students: Andrew Lobb and Bihong Zhang



Professor Ray Rodgers



Ovarian Development

Ovarian development and its role in fertility and endocrine function

In addition to its obvious role in fertility, ovarian function affects many other physiological systems in women and plays a role in systemic disease. Polycystic Ovary Syndrome (PCOS) is a common endocrine

disorder, affecting approximately one in 20 women of reproductive age. Affected individuals suffer infertility, symptoms of excess androgens and are predisposed to developing obesity, type 2 Diabetes and dyslipidaemia. Recent studies suggest that the biological predisposition to developing PCOS is established in the fetal ovary, and involves the transforming growth factor (TGF)-beta pathway. It is possible that TGF-beta is key in development of many organ systems during fetal life: this would explain the diverse metabolic complications observed in women with PCOS. The Ovarian Development Group conducts research to investigate how the ovary develops, with a view to understanding the fetal origins of PCOS and how androgen production is regulated in adult ovaries.

During 2012, the Group achieved a breakthrough in generating novel data describing a new cell population in fetal ovaries (gonadal ridge epithelial-like cells), the origins of ovarian stromal cells and the formation of ovarian tissue compartments. A new model describing how ovaries develop

has been published based on this work. Additional work conducted during 2012 addressed the:

- > Role of maternal diet in altering growth of the fetus through altered TGF-beta-regulated gene expression and epigenetic changes
- > Role of specialised extracellular matrix in regulating the maturation of follicular granulosa cells
- > Identification of cell fate decisions in fetal ovaries
- > Identification of a stromal stem cell niche in adult ovaries

Group members

Postdoctoral Researcher: Katja Hummitzsch

PhD Candidate: Katrina Copping

Honours Student: Isabella-Rose Meredith

Research Assistants: Wendy Bonner, Nicholas Hatzirodos and Yvonne Miels

Associate Professor Darryl Russell



Ovarian cell biology

Ovarian and reproductive cancer cell biology

Statistics show that one in six Australian couples are unable to naturally conceive a pregnancy. Maternal factors contribute to infertility as a result of abnormalities in the cellular and molecular communication networks that operate between developing oocytes, the ovarian follicles that nurture them and the reproductive tract. The Ovarian Cell Biology Group conducts

research to determine how the integrated context of tissue structure and intercellular communication factors controls the selection and maturation of oocytes in the ovary. Group members are also interested in extrapolating their findings to investigate cancers of reproductive organs. This complementary line of work stemmed from the discovery that mechanisms involved in remodeling ovarian follicles have aspects in common with processes through which cancers become metastatic.

The Group achieved several key findings during 2012:

- > The demonstration that cumulus-oocyte complexes in ovulating ovaries transiently adopt highly invasive capacity. This finding provides entirely new insight into ovulation, showing for the first time a hormone-controlled mechanism through which cumulus cells mediate oocyte release. Further development of this work will target the regulatory role of the oocyte, with implications for understanding and treating infertility
- > A unique discovery on the mechanism of oocyte – cumulus cell communication, which showed that the oocyte secreted growth factor GDF9 interacts with

abundant extracellular matrix structures that are regulated by reproductive hormones. Through this mechanism, maternal hormones and the cumulus extracellular matrix modulate oocyte signaling to ovarian somatic cells. This insight has applications in improving assisted reproductive techniques

- > The demonstration that breast cancer metastasis requires a protease gene called ADAMTS1. Inactivating this gene dramatically reduced cancer invasive capacity and metastasis to lung. This finding is now being developed further as a possible diagnostic tool to identify patients at elevated metastatic risk, and for clinical adjuvant therapy to control patient relapse

Group members

Research Leader: Rebecca Robker

Postdoctoral Researcher: Kylie Dunning

Postdoctoral Affiliate: Kathryn Gebhardt

Research Officer: Laura Watson

PhD Candidates: Lisa Akinson and Izza Tan

Honours Student: Adrian Kamil Kaczmarek

Research Assistants: Jamie Voueleng Zhang

Visiting Scientist: Dr Yan Meng

Associate Professor Jeremy Thompson



Early Development

Early life programming of fetal development and adult health

Accompanying fertilisation are dynamic molecular and biochemical processes that have a major impact on subsequent embryonic and fetal development, as well as adult health. The newly fertilised egg is extremely sensitive to the microenvironment within the maternal reproductive tract, and this is reflected in a process of 'resetting' of its epigenetic code. If the metabolic microenvironment surrounding the oocyte and embryo is altered as a result of diet and lifestyle factors, this will influence the epigenetic mechanisms that ultimately

control the growth rate and developmental potential of the resulting fetus. The Early Development Group conducts research to better understand the link between altered metabolic states within oocytes and embryos and epigenetic mechanisms controlling growth. During 2012, the Group achieved a number of research goals. A unique finding was the discovery of regulated levels of haemoglobin within oocytes, and that during in vitro maturation oocytes lose their haemoglobin content. In addition, Group members working with a diabetic mouse model 'mapped' the influence of hyperglycemia on oocyte and cumulus cell protein levels of O- β -linked glycosylation. This post-translational

modification is regulated within oocytes by the activity of the hexosamine biosynthesis pathway and the X-linked enzyme, O-glycosyltransferase. Results showed that a major target protein is heat shock protein-90: inhibiting this chaperone protein returned normal developmental competence to oocytes during in vitro maturation. Members also characterized the role of bone morphogenesis protein-15 – an oocyte secreted factor known to improve oocyte competence in vitro – on cumulus-oocyte complex metabolism.

Group members

Postdoctoral Researchers: Deanne Feil, Hannah Brown and Melanie McDowall

Research Scientists: Xiaoqian Wang, Annie Whitty and Samantha Schultz

PhD Candidate: Laura Frank

Honours Students: Siew Wong and Luisa Cavuolo

“ The newly fertilised egg is extremely sensitive to the microenvironment within the maternal reproductive tract ”

Centre for Stem Cell Research

One of the important practical technologies to emerge from reproductive biotechnology is stem cell therapy. These cells hold enormous promise for new treatments in a range of devastating childhood and adult diseases including stroke, diabetes, leukemia and more

Directors' report

The Centre for Stem Cell Research is at the forefront of stem cell research and medicine in Australia.

Working at the cutting edge of stem cell science, the Centre is uniquely placed to drive the development of new clinical treatments. This occurs by application of a multifaceted approach and working with a network of local, national and international collaborations.

The Centre for Stem Cell Research is made up of 20 unique groups. Groups are united by key research themes that include: stem cell biology, cell therapy, tissue and organ transplantation and blood cancers.

Members undertake internationally recognised and awarded research into stem cells found in bone marrow, neural tissues, the periodontium, the ovary and cord blood. Working across these areas, the Centre focusses on the development of clinical applications for children and adults in:

- > Stroke repair
- > Cardiac repair
- > Tissue repair, including dental structures, muscles and cartilage
- > Cystic fibrosis



- > Lysosomal storage and other inherited disorders
- > Transplantation medicine
- > Developmental biology
- > Immune diseases
- > Leukaemia

The breadth of the work and capacity to bring together scientific and medical expertise is evidenced by the Centre's presence in key South Australian research institutions including:

- > The University of Adelaide
- > Hanson Institute
- > Women's and Children's Hospital
- > SA Pathology
- > Queen Elizabeth Hospital
- > Royal Adelaide Hospital
- > South Australian Research and Development Institute (SARDI)

The calibre of the research is also reflected in the many collaborative projects conducted with top stem cell scientists across Australia and the world. The Centre also maintains strong commercial relationships - including with regenerative medicine company Mesoblast Ltd (Melbourne and New York).

In 2012 the Centre for Stem Cell Research expanded to welcome two new groups of members focussing on stem cells in neuronal development and animal reproduction. These additions reflect the continuing drive to conduct first class collaborative stem cell research with a view to supporting the development of new clinical cell-based treatments.

Professor Stan Gronthos and Associate Professor Mark Nottle, Co-Directors

Professor Mark Bartold

Periodontal Repair

Mesenchymal stem cells for regeneration of structures affected by periodontal disease

Periodontitis is a disease of the periodontium – the specialised tissues that surround and support the teeth – and is characterised by irreversible loss of connective tissue attachment and supporting alveolar bone. These changes often lead to loss of tooth function and aesthetic changes to the mouth and dentition. Regeneration of tissues damaged by periodontitis has been an elusive goal in clinical periodontics. To date, repair of damaged periodontal tissues relies on implantation of structural substitutes with little or no reparative potential. Tissue engineering involving the use of stem cells to regenerate and repair the periodontium offers an alternative to existing therapies for periodontal regeneration.

The Periodontal Repair Group focuses on novel approaches to the surgical implantation of mesenchymal stem cells at sites of periodontal destruction to achieve tissue repair for restored tooth function and appearance. The Group has achieved considerable success in using mesenchymal



stem cells for periodontal regeneration in experimental defects in both small and large animals. Current research activities are focused on investigating the preclinical utility of induced-pluripotent stem cells as an alternative source of cells for these regenerative procedures. The lessons learned are relevant to mesenchymal stem cell applications for tissue in a broad range of diseases.

Group members

Professor: Stan Gronthos

Research Staff: Victor Mariono and Jia Ng

Senior Lecturer: Peter Zilm

Postdoctoral Researchers: Kim Hynes, Danijela Menicanin and Atsushi Tomokiyo

Dr Claudine Bonder



Vascular Development

Understanding blood vasculature and its role in health and well-being

Delivery of blood occurs via an intricate network of vessels distributed around the body. As well as sustaining bodily functions

under normal conditions, blood vessels are essential to support tissue regeneration, organ transplantation and the progression of many diseases affecting children and adults. Improved understanding of how blood vessels form and the control of their development may provide therapeutic opportunities and great public health potential. The Vascular Development Group focuses on blood vessel development as it relates to immune dysfunction and disease. The group is particularly interested in stem like-cells known as endothelial progenitor cells, which directly contribute to blood vessel formation in physiological repair processes and pathological settings such as cardiovascular disease, cancer, diabetes, arthritis and ischemia/reperfusion injury.

In 2012 the Group achieved several key research goals:

- > Identification of new surface expressed proteins on human endothelial progenitor cells. These are now being examined for their potential to attenuate blood vessel development in cancer

- > Finding that co-transplantation of endothelial progenitor cells with pancreatic islets significantly improves the cure rate in a mouse model of diabetes. This research was performed in collaboration with Dr Claire Jessup (Flinders University) and Associate Professor Toby Coates (Royal Adelaide Hospital)
- > Identification of a key regulatory enzyme in the early phase of allergic inflammation. New therapeutic approaches for allergy are now being developed based on this work, which was performed together with Associate Professors Stuart Pitson and Michele Grimbaldston (Centre for Cancer Biology).

Group members

Postdoctoral Researchers: Lisa Ebert, Lachlan Moldenhauer and David Dimasi

Research Assistants: Michaelia Cockshell and Emma Thompson

PhD Students: Kate Parham, Wai Yan Sun and Lih Tan

Technical Officer: Samantha Escarbe

Associate Professor Toby Coates



Transplantation

Novel cell based therapies to treat organ failure and provide immunosuppression

Organ transplants are one of the major triumphs of modern medicine but are plagued by side effects of associated immunosuppressive drug therapy, which damages their function and longevity. Cell therapy using donor tissue is relevant to a range of autoimmune and other diseases affecting children and adults, such as type-1 diabetes.

The Transplantation Group seeks to use different cell types as transplant therapy to:

- > Replace function (pancreatic islet cells to treat type-1 Diabetes)
- > Repair blood supply to transplanted organs (endothelial progenitor cells)
- > Induce immunosuppression without drugs (mesenchymal stem cells and dendritic cells)

In 2012 the Group expanded previous work to apply endothelial progenitor cells in transplant models to improve the blood supply for transplanted islets. In addition, a new means to protect islets by transfecting them with anti-apoptotic factors was identified - improving survival of the transplants. The Group also focused on improving the immunosuppressive potential of mesenchymal stem cells.

To continue advancing the work of the Transplantation Group, an application to become a Collaborative Research Centre in Cell Therapy Manufacturing was submitted during 2012, and this has now been successfully funded. The Group also published eleven peer-reviewed publications, including a paper in the well-regarded British Medical Journal on the use of colonoscopy to screen for colorectal cancer in kidney transplant recipients. This work was the first study to show that colonoscopy is the preferred mode of screening in this population, and was highlighted in the journal's editorial feature and received wide media attention.

Group members

Research Heads:

Shilpa Jesudason and Rob Carroll

Principal Medical Scientist: Christopher Drogemuller

Senior Medical Scientist: Sveltana Kireta

Research Scientist: Daniella Penko

Technical Officer: Julie Johnston

Collaborators:

Claudine Bonder and Shane Grey

Postdoctoral Researchers: Claire Jessup and Daisy Mohanasundaram

PhD Candidates: Mariea Dency-Bosco, Michael Collins, Chris Hope, Amy Hughes and Kisha Sivanathan

Professor Richard D'Andrea, Associate Professor Ian Lewis

Acute Leukaemia

Identification and characterisation of genes involved in the myeloid lineage and in myeloid disease

Acute myeloid leukaemia accounts for 20% of leukaemia in children and is the most common form of acute leukaemia in adults, and can have devastating clinical prognosis. Overall survival for adult acute myeloid leukaemia is still only 30-40%, and for certain subtypes median overall survival is just 10 months. The disease results from the accumulation of immature myeloid cells (blasts) in the bone marrow and peripheral blood, and is heterogeneous in nature. Although several disease subtypes have now been classified according to their molecular aberrations, the molecular basis for many subtypes is still unknown and key targets for therapy are still being identified. As a result, the capacity of clinicians to select more effective treatment is still suboptimal. Consequently, there is a clear need to improve patient stratification to select the best available treatments for each patient, and also to develop new therapies targeted to the specific patient groups.

The Acute Leukaemia Group aims to understand the mechanisms underlying normal blood cell growth and differentiation, and the changes associated with myeloid diseases such as acute myeloid leukaemia.



Professor Richard D'Andrea

During 2012, the Group's research activities focused on:

- > Identification of a novel role for a gene called TCF4 in normal blood formation
- > Investigation of the prognostic impact of promoter methylation of the KLF5 and GADD45A genes in a cohort of acute myeloid leukaemia patients. These studies will help assist with patient stratification to better select treatment options
- > Identification of acquired gene mutations in genes including DNMT3A in patients suffering from a group of pre-leukaemic haematological diseases known as myeloproliferative neoplasms

- > Identification of novel pathways that may be targeted to induce death of diseased cells in acute myeloid leukaemia and myeloproliferative neoplasms, and inhibitors of these pathways. This line of research may identify effective, targeted treatments to improve patient outcomes

Group members

Senior Research Officer: Anna Brown

Research Officer: Sonya Diakiw, Chung Kok and Michelle Perugini

Postdoctoral Fellow: Sarah Bray

Senior Research Assistant: Carolyn Butcher

PhD Candidates: Nisha Rao, Teresa Sadras and Nur Hezrin Shahrin

Honours Students: Kyaw Zeya Maung

Research Assistants: Grant Engler, Diana Larossi, Nick Li and Amelia Wee



Professor Simon Koblar



Stroke

Stem cells as a therapy for improved outcomes in ischemic stroke

As many as 60,000 Australians suffer a stroke every year and one third are left with severe disability. One therapeutic strategy for treating stroke is to transplant adult tissue-derived stem cells that have the ability to differentiate into neurons and replace the function of damaged cells. The Stroke Group aims to improve stroke outcomes by administering stem cells derived from the dental pulp of the human tooth – having previously demonstrated in rats that dental pulp stem cells injected into the brain can improve neurological function after stroke.

“ This research has the potential to lead to a new treatment using dental pulp stem cells ”

In 2012, the Group began a pre-clinical trial aimed at improving the neurological function of mice affected by stroke. This model is more clinically relevant than that developed previously, as it involved intravenous rather than direct brain administration of the stem cells. Twenty-four hours after stroke, dental pulp stem cells were administered intravenously, and the ability of mice to use their stroke-affected limbs and whiskers was evaluated. This study is now two-thirds completed, with members looking forward to determining whether dental pulp stem cell treatment can improve stroke outcomes in this model. This research has the potential to lead to a new treatment using dental pulp stem cells, which could aid in patient recovery after stroke.

At the end of 2012, through Adelaide Research and Innovation, a contract for collaboration and clinical translation of the animal stem cell studies in stroke to a future clinical trial was finalised with Mesoblast Ltd. (Melbourne, Australia). This research will be lead by Simon Koblar.

Group members

Principal Medical Scientist and Management Coordinator and Co-Director Stroke Research Program, Basil Hetzel Institute: Anne Hamilton-Bruce

Neurologist/Stroke Researcher: Jim Jannes

Peter Couche Foundation Postdoctoral Research Fellow: Karlea Kremer

Postdoctoral Research Fellow: Thomas Klaric and Martin Lewis

PhD Candidates: Fong Chan Choy, Michael Djukic, Wai Khay Leong, Elaine Leung and Kylie Ellis

Medical Students: Joule Juan Li and Rebekah Chew

Master of Medical Science Student: Wenru Pan

Honours Students: Joshua Winderlich and Adam Humenick

Research Assistant: Xenia Kaidonis

Professor Stan Gronthos



“ Mesenchymal stem cells have potential as novel therapeutic agents for repairing damaged connective tissue ”

Mesenchymal Stem Cells

Origins and biological properties of mesenchymal stem cell populations

Bone marrow is thought to contain a population of self-replicating multi-potential stem cells referred to as mesenchymal stem cells. Mesenchymal stem cells have potential as novel therapeutic agents for repairing damaged connective tissue due to trauma, disease or congenital conditions.

The Mesenchymal Stem Cell Group, in collaboration with Professor Zannettino, has developed novel stem cell isolation technology to identify mesenchymal stem cell-like cells from adipose tissue and dental tissues that exhibit similar growth properties and gene expression profiles to those identified in bone marrow. This work has resulted in the generation of several patents encompassing the isolation and expansion technologies and use of different mesenchymal stem cell preparations for various tissue engineering based applications. These patents have now been licensed to two sister companies: Angioblast Inc. (New York, NY) and Mesoblast Ltd. (Melbourne, Victoria).

The Mesenchymal Stem Cell Group is now the leading group worldwide with the technology to purify mesenchymal stem cells directly from human tissue using its

own patented isolation protocols. Work conducted during 2012 has addressed:

- > Identification of epithelial derived cell populations in dental structures capable of undergoing transition into mesenchymal stem cells
- > Demonstration that specific epigenetic changes in mesenchymal stem cells control cellular senescence and life span
- > Pre-clinical studies demonstrating efficacy of mesenchymal stem therapy in ischaemic stroke, cardiac disease, intervertebral disk degeneration and periodontal disease
- > Identification of factors central to mesenchymal stem cell-mediated regulation of haematopoiesis, angiogenesis and immune cell modulation, with potential implications in understanding tumour cell development

Together with commercial partner Mesoblast Ltd., the Mesenchymal Stem Cell Group is moving forward into Phase II/III human clinical trials for orthopaedic and cardiovascular applications using mesenchymal stem cells. Furthermore, Phase II/III human trials are being conducted to assess the efficacy of ex vivo expanded cord blood on mesenchymal stem cell feeder layers for the reconstitution of bone marrow in cancer patients following ablative therapy.

Continuing research into the basic properties of mesenchymal stem cells will help develop effective and safe therapeutic strategies in the future for a wide variety of clinical indications.

Group members

Research Fellow: Agnes Arthur

Postdoctoral Researchers: Dimitrios Cakouros and Esther Camp-Dotlic

Research Assistant: Romana Panagopoulos

Technical Officer: Sharon Paton

PhD Candidates: Lachlan Cooper, Sarah Hemming and Thao Nguyen

Honours Student: Yi Yan Janice Lim

Associate Professor Mark Nottle

Reproductive Biology

Reproductive biology for biomedical and agricultural applications

Scientists now have the capacity to work with embryonic stem cells isolated from pre-implantation embryos of mice and humans. These cells can be differentiated into all the cell types in the body and hold considerable promise in providing cures for a range of diseases and injuries in humans. In collaboration with national and international research bodies, research is focused on developing organ, tissue and cell replacement therapies. As human embryonic stem cell research advances to the clinic, there is a need to develop a large animal model for this research. The Reproductive Biology Group is focused on the isolation of porcine embryonic stem cells from in vitro-produced, cloned and parthenogenetic embryos in order to model human stem cell research applications. This work is funded by various agencies including the National Health and Medical Research Council, the Juvenile Diabetes Research Foundation and industry.



During 2012, the Reproductive Biology Group isolated and characterised stem cells from parthenogenetic porcine embryos. Porcine induced pluripotent stem cells were also isolated, and are currently being investigated further in a joint project with Professor Paul Verma at the South Australian Research and Development Institute. Other work conducted in 2012 focused on improving the quality of embryos generated in vitro and reducing early embryonic loss in animals.

Group members

Centre Manager: Leanne Srpek

Research Fellow: Ivan Vassilev

PhD Candidates:
Jared Campbell and Robert Smits

Honours Students: Anders Tsui

Research Assistants:
Stephen McIlfratrick and Emmy Bouwman

Associate Professor David Parsons



Cystic Fibrosis

Development of gene therapy for prevention or treatment of cystic fibrosis

Cystic fibrosis is a relatively common chronic illness in children that reduces lifespan to young adulthood through its impact on the lungs and other organ systems. The disease is autosomal recessive, resulting when two faulty copies of a gene known as CFTR are

inherited - one from each parent. The Cystic Fibrosis Research Group aims to develop an effective genetic therapy for prevention or treatment of cystic fibrosis airway disease. Research activities are focused on achieving effective lentiviral CFTR vector gene delivery, transduction of airway stem cells in situ to enable extended gene expression, and development of rapid and accurate outcome measures for assessment of airway disease and the effects of novel therapeutics.

Group research conducted during 2012 was centred on developing novel synchrotron-based techniques for assessing airways physiological function. A collaborative project with physicists from Monash University and the Australian Synchrotron was established to develop novel X-ray imaging approaches effective in living mouse airways. This approach is now under development for translation into a potential human application.

Working with a mouse model of cystic fibrosis, experimental studies were also performed at the Spring-8 synchrotron in Japan during 2012. The technology allowed visualisation of lung mucociliary transit by tracking the movement of inhaled particles over time. The impact of pharmaceutical

treatments on mucociliary transit and airway surface liquid depth (a critical controller of airway health) could then be assessed. A large amount of very promising imaging data was captured; analysis of those results continues now. Using the same model, gene therapy studies uncovered preliminary but exciting indications that delivery of correctly-functioning CFTR genes into the affected airways of mice results in increased survival. This appears to be the first time that cystic fibrosis gene therapy has shown a survival benefit. Current Group work is focused on extending and confirming these exciting early results.

Group members

Postdoctoral Research Fellow: Martin Donnelley

Postdoctoral Scientist: Patricia Cmielewski

PhD Candidates: Nigel Farrow, Harsha Padmanabhan and Ryan Green

Honours Student: Jahan Penny-Dimri

Research Administration Manager:
Corinne Reynolds

Dr Quentin Schwarz



Neurovascular Research

Molecular mechanisms controlling neuronal and vascular development

Embryonic development is a fascinating process that relies on dynamic and precise cellular growth mechanisms to establish key organ systems. The neuronal and vascular systems are particularly critical for survival, and rely heavily on each other to become positioned correctly for adult physiological processes and to provide trophic support to instruct specified bodily functions. Aberrant development of neurons or blood vessels gives rise to a wide spectrum of disorders that are important from a public health perspective, such as schizophrenia, autism, diabetes and cardiovascular disease.

The primary objective of the Neurovascular Research Group is to define the molecular events that control embryonic development, with a particular focus on the neuronal and vascular systems. Understanding how these systems form in normal development will offer novel insights regarding what goes wrong in pathological conditions, and uncover new potential therapies.

The Neurovascular Research Group made significant inroads to these research questions during 2012. Research members uncovered a new risk factor for schizophrenia and related disorders: assessment of 14-3-3zeta expression or function and its role in 14-3-3zeta / DISC1 interaction. This pathway is believed to be extremely promising for establishing a definitive diagnostic test for schizophrenia and other related disorders. This finding also offers insights regarding the molecular pathways underpinning schizophrenia and other related disorders, and provides key targets for the development of novel therapies. This work was published during 2012 in the highest-ranking journal in the psychiatry field, *Molecular Psychiatry*.

Group members

Postdoctoral Researcher: Sophie Wiszniak

Research Assistants: Samueala Kabbara, Michaela Scherer and Xiangjun Xu

PhD Students: Rachael Lumb, Eiman Saleh

Professor Paul Thomas



Neural Development

Genetic basis and pathology of disorders that affect the nervous and reproductive systems

Disorders of the nervous and reproductive systems are among the most common childhood conditions. Mental retardation – the most frequent cause of serious disability in children and young adults – often results from mutations in genes that are critical in formation of the central nervous system during embryonic development. Similarly, key genes play a role in the differentiation of

fetal reproductive tissues into male or female sexual organs. Working with embryonic stem cells and neuroprogenitor cells to develop in vivo and in vitro model systems, research conducted by the Neural Development Group examines the genetic causes of abnormalities in the central nervous and reproductive systems.

Focusing on key genes involved in neurological disease, the Group has established mouse models that are providing unique insights into the genetic control of brain development and the biological basis of mental retardation and

hydrocephalus. Congenital hydrocephalus is a life-threatening medical condition in which excessive accumulation of cerebrospinal fluid leads to ventricular expansion and increased intracranial pressure. Data published by the Group this year showed that a subtle defect in brain development due to gene over-expression can result in hydrocephalus in mice.

In 2012 the Group also established a unique mouse model of sex reversal in which chromosomally female mice develop as males. These mice are providing exciting new insights into the evolution and molecular mechanism of sex determination in mammals. Furthermore, in collaboration with Dr David Chitayat (University of Toronto, Canada), a unique rearrangement of the SOX3 gene was identified in an individual with XX male sex reversal. These data build on previous research in this field and highlight SOX3 rearrangements as one of the leading causes of this condition.

Group members

Postdoctoral Researcher Fellow: James Hughes

Lecturer: Bryan Haines

PhD Candidates: Kristie Lee, Dale McAninch and Nicholas Rogers

Honours Student: Daniel Pederick

Research Assistant: Sandie Piltz

Professor Stephen Worthley

Cardiac Repair

Treatment of cardiovascular disease using stem cells and other approaches

Heart failure resulting from weakened heart muscle is a key cause of ill health and death in Western societies. Once damaged or dying due to lack of blood supply (as occurs in myocardial infarction) or other causes such as viruses and toxins, heart muscle cells do not have the capacity to repair themselves. As a result, treatment options are limited. Recently, different types of stem cells have been studied as a way of regenerating and repairing injured cardiac tissue. Mesenchymal stem cells are a rare type of bone marrow cell that have the ability to divide and self-renew. The Cardiac Repair Group is interested in exploring the potential of mesenchymal stem cells to develop into heart cells and be used to treat patients with heart failure. The Group also performs research relating to a broad range of other cardiovascular diseases, their pathology, management and prevention. Overall aims are to enhance the understanding of disease processes and develop effective and minimally-invasive therapies.

In 2012 Group members continued several pre-clinical study programs to explore optimal timing and dosage of mesenchymal stem cell therapy for the treatment of acute myocardial infarction.

Other 2012 Group activities relating to cardiovascular conditions were as follows:

- > Completion of the first 'in man' trial of percutaneous intra-vascular radio frequency ablation of renal artery nerve fibres for the treatment of resistant hypertension as part of the EnligHTN Trial. Data released to date demonstrates clinically significant reduction of blood pressure levels with nil adverse affects



- > Commencement of novel angiographic studies which incorporate baseline and follow up intra-vascular ultrasound coupled with near infrared spectroscopy to analyse and monitor cardiovascular plaque burden and compositional changes, and reconcile these with changes in how coronary arteries respond to administration of vaso-active agents. Such studies provide crucial insights into patient disease status
- > Continuation of trans-aortic valve implant procedure studies in which prosthetic aortic valves can be introduced and deployed through the femoral artery via a small skin incision, as an alternative to open heart surgery

Group members

Senior Research Fellow: Angelo Carbone

Research Fellow: Adam Nelson

Interventional/MRI Fellows: Seng Keong Chua and Viji Thomson

Interventional Fellows: Tim Glenie, Samuel Sidharta (also PhD candidate)

MRI Fellow: Luay Samaraie

Cardiac MRI Technologists: Ben Koschade and Kerry Williams

Senior Lecturers: Karen Teo and Matthew Worthley

PhD Candidates: Dennis Wong, Lachlan Frost, Rishi Puri, Ararishan Shah, Tim Baillie and James Richardson

Medical Student: Michael Weightman

Administration Officer: Angela Hooper

Professor Andrew Zannettino



Myeloma Research

Molecular and cellular mechanisms underlying the pathogenesis of multiple myeloma

Multiple myeloma is an incurable haematological malignancy characterised by the clonal proliferation of malignant plasma cells within the bone marrow. The disease is the second most common haematological malignancy after non-Hodgkin's Lymphoma, with approximately 1,400 newly diagnosed patients each year in Australia. Despite recent advances in treatment, multiple myeloma remains almost universally fatal with a five-year survival rate of approximately 30%. The main clinical manifestations of multiple myeloma are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased bone marrow angiogenesis. It is now widely accepted that most, if not all, multiple myelomas

preceded by a premalignant stage known as MGUS: monoclonal gammopathy of uncertain significance. However, the genetic factors that trigger the progression from asymptomatic MGUS to overt malignant multiple myeloma remain to be determined.

A number of key research outcomes have been achieved by the Group in 2012 including:

- > Identifying key genetic changes that 'drive' the progression from asymptomatic MGUS to overt malignant multiple myeloma
- > Identifying novel bone marrow microenvironmental factors that contribute to multiple myeloma disease progression
- > Identifying novel signaling pathways with roles in mesenchymal stem cell differentiation which may be manipulated to increase bone formation in multiple myeloma patients
- > Identifying that plasma N-cadherin levels can be used as a prognostic marker for high-risk multiple myeloma patients.

Group members

Postdoctoral Scientists: Stephen Fitter, Duncan Hewett, Jacqueline Noll, Kate Vandyke and Sharon Williams

Research Fellow: Sally Martin

PhD Candidates: Catherine Gan, Mary Matthews, Krzysztof Mrozik, Carmen Macsai, James Richardson, Natalia Martin, Lachlan Cooper and Furqan Ahmed

Research Assistants: Sharon Paton and Vicki Wilczek

Honours Students: Chee Man Cheong and Tony Le

Contributing Clinician: Annie Chow



Translating our research

The Robinson Institute aims to transform the health of children and families across generations and global communities. In 2012 the Institute continued to make international impact through its research discoveries, translation into clinical care and policy and a range of commercial developments

Discovery of new cell challenges old assumptions about the ovary

Looking down a microscope at an adult ovary reveals a fascinating and very precisely-organised tissue.

The structural integrity of the ovary is critical to ensure regular release of healthy eggs and production of hormones essential for women's health. Understanding how the structures in the adult ovary come about is therefore critical for assisting women with fertility problems, and to address diseases such as polycystic ovary syndrome and ovarian cancer. During 2012 Ray Rodgers from the Robinson Institute's Ovarian Development Group discovered a new cell type in ovaries. The discovery challenges decades old assumptions about how ovaries develop, and may have therapeutic implications.

After puberty, the ovaries play an important role in many aspects of female health. In addition to maturing eggs in tissue compartments known as follicles, the ovaries produce oestrogen and progesterone that maintain healthy tissues throughout the female body in both the pregnant and non-pregnant state. When the structure and function of the ovary breaks down, reproduction can fail and other effects can be widespread.

Head of the Robinson Institute's Ovarian Development Group, Professor Ray Rodgers has spent the majority of his career looking at how ovaries function in health and disease. For Ray, like others in his field, research was guided by basic assumptions regarding how ovaries form.

"For more than a decade, scientists believed that ovarian granulosa cells – the cells that surround developing eggs in follicles and produce oestrogen – were derived from the epithelial cells on the surface of the ovary," said Ray.

In 2012 Ray, along with postdoctoral fellow Katja Hummitzsch and other colleagues, uncovered a new cell type in cow ovaries that turns this assumption on its head.

The cells, referred to as GRELs (Gonadal Ridge Epithelial-Like cells), were first observed whilst studying cultures of dispersed fetal calf ovaries. Katja and Ray tracked the development, multiplication and behaviour of GRELs within the early ovary. They found that concurrent with other structural changes, the GRELs are partitioned into small sub-groups of cells. One sub-group is associated with the developing eggs (the oocytes) and another sub-group accumulates towards the external aspect of the ovary. Each of these sub-groups then develops further to become the oestrogen-producing granulosa cells and the surface epithelium respectively.

Now published in the open access journal PLOS ONE, the finding has fundamentally changed the way Ray thinks about the ovary.

"We realise now that what is in the textbooks on how the ovary develops is not correct," said Ray.

The research is a very exciting, once-in-a-career type breakthrough that many scientists don't ever manage to achieve.

"Having studied ovaries nearly all my career, for my research group to have discovered a new cell type which offers key insight into how these complex organs develop is really something special for me," he added.

Achieving this end result was only possible thanks to lengthy and detailed groundwork. It took Ray, Katja and their colleagues several years to develop the appropriate tools to properly identify and track the

GREL cells, and to distinguish them from other cells also present in ovaries. This was accomplished by growing and studying cells from developing cow ovaries in the laboratory, and undertaking very detailed analyses of the cell populations and non-cellular structural compartments of ovaries as they developed over time.

"A number of small steps lead us to the complete story," said Ray.

If the same processes also occur in human ovaries, there are many potential implications of this work for women's health, particularly in conditions such as premature ovarian failure and ovarian cancer. Polycystic ovary syndrome, or PCOS, which is often associated with disruptions in the structure of the ovary, is likely to be one area of focus for Ray moving forward.

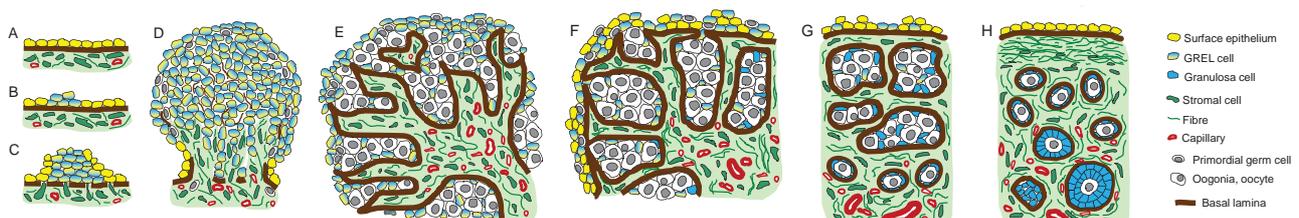
"The PCOS ovary is associated with an increased number of growing follicles that at some point just stop working," said Ray. "This new knowledge may help us to unravel the origins of this very common clinical syndrome."

However Ray admits it's early days yet.

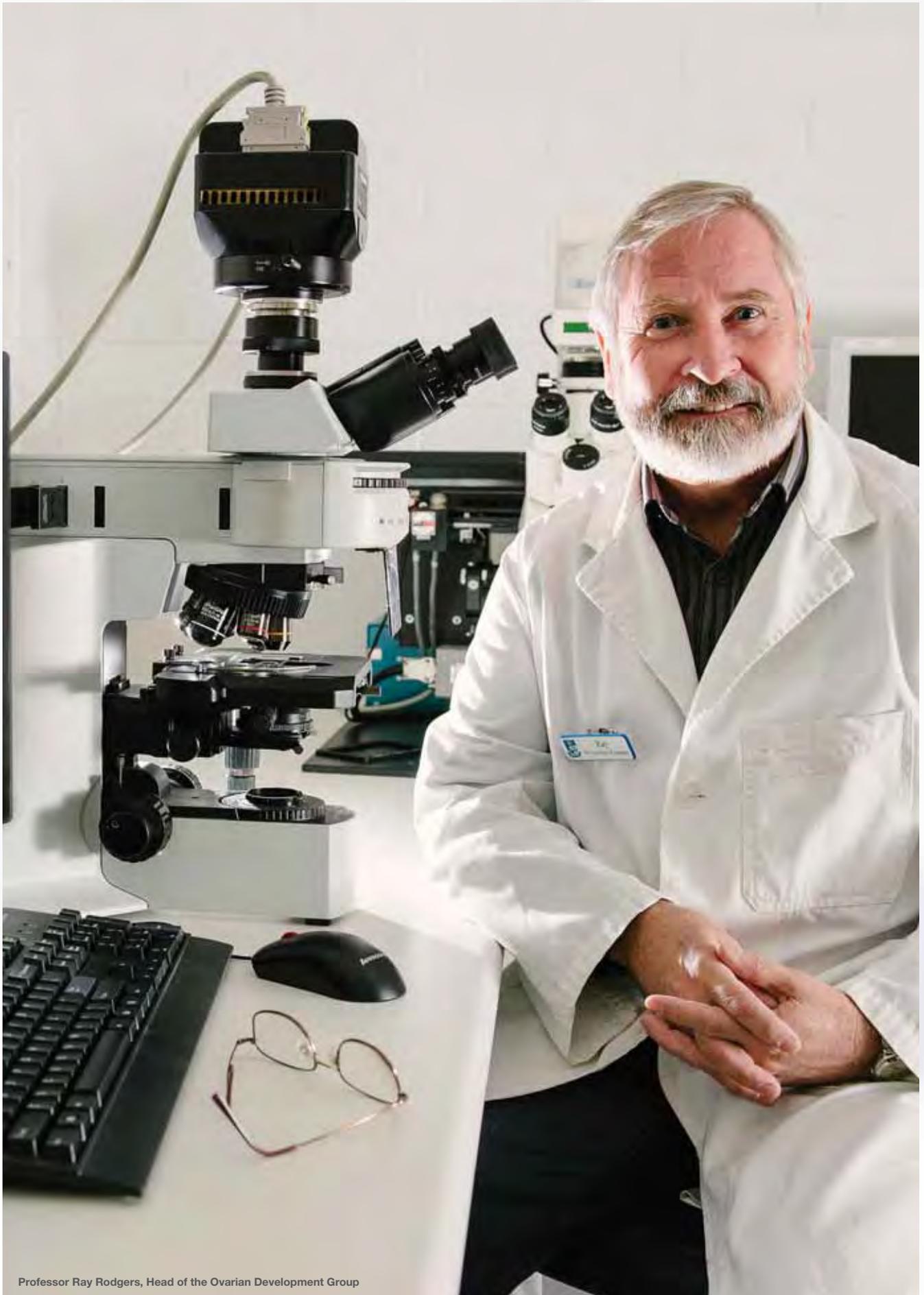
"While the research helps our understanding of how follicles develop in cows and shows that the process is relatively simple, a lot more research is required to understand the regulation of key cells in women," he said.

"At least we are now on the correct path to discovering more about how the ovaries and their follicles are formed."

This research was funded by the National Health and Medical Research Council of Australia, the University of Adelaide, the Clive and Vera Ramaciotti Foundation and the Australian Research Council.



Proposed model of the formation of the bovine ovary as published in [Hummitzsch K et al. (2013) A new model of development of the mammalian ovary and follicles. PLoS One. 2013;8(2):e55578. DOI: 10.1371/journal.pone.0055578.]



Professor Ray Rodgers, Head of the Ovarian Development Group

How genes and lifestyle factors interact to determine pregnancy health

Although lifestyle factors such as poor diet and smoking are known to impact negatively on pregnancy, health carers cannot yet identify which mothers and babies are most susceptible to their influence.

Improved understanding of how life choices interact with maternal and paternal genes would allow targeted and cost-effective obstetric care to be provided to high-risk mothers and babies.

The Robinson Institute's Placental Development Group is exploring the interactions between genes and lifestyle factors to better understand and prevent pregnancy complications such as preeclampsia, intrauterine growth restriction and premature delivery.

Recurrent miscarriage, preeclampsia, small-for-gestational age pregnancy and preterm birth together complicate as many as 22% of all pregnancies. On top of the emotional turmoil resulting from these conditions, there are significant associated health costs for mothers and babies during and after pregnancy, and for the remainder of life. Opportunities to identify and manage pregnancies at highest risk of enduring these conditions will offer a significant public health benefit.

Claire Roberts, Co-Director in the Placental Development Group, is interested in how subtle variations in genes, known as polymorphisms, impact on pregnancy. Gene polymorphisms aren't usually clinically obvious, and can only be detected in the cells of patients using very specific analytical techniques.

"We've spent some time now looking at associations between gene polymorphisms and risks of adverse birth outcomes. During 2012 we started to look at the lifestyle factors, and how they may be involved," she explained.

"We've now published interesting data showing associations between poor pregnancy outcomes and certain gene polymorphisms combined with aspects of maternal nutrition."

The new studies focused on the following pregnancy outcomes: babies who were

born pre-term or small-for-gestational age, and preeclampsia, a condition characterised by high maternal blood pressure and poor function of the mother's kidneys and other organs.

Several of these associations emerged from studies conducted by PhD candidate Ang Zhou, who looked at polymorphisms in genes involved in blood pressure regulation. He found that maternal polymorphism in one key gene was associated with delivering a small baby. Interestingly, however, the association only held true for a subpopulation of women carrying the particular polymorphism - those classified as being of low socioeconomic status, who consumed less than one serve of leafy green vegetables a day in pre-pregnancy and who delivered a female infant.

In a separate publication, Ang also reported an association between a polymorphism in a second gene involved in blood-pressure regulation and increased likelihood of preeclampsia, but only in women who were overweight or obese.

Finally, postdoctoral research fellow Denise Furness published her data showing that maternal folate intake in early pregnancy is associated with increased likelihood of pre-term birth and delivery of a small-for-gestational age infant.

Together, the studies suggest that adverse outcomes such as pre-term birth, small-for-gestational age infants and preeclampsia have a genetic basis that is modifiable by dietary and possibly other environmental exposures.

"The simple message seems to be that if key genes are having an impact on pregnancy outcomes, the effect is subtle. If you look after your health, they may not necessarily come into play. If you eat poorly or become overweight, it may be a different story," suggests Claire.

"We recommend future studies should take into consideration clinical and lifestyle factors, as well as fetal sex, in order to explain the genetic associations more clearly."

For now however, there are some simple clinical implications arising from this work.

"Regardless of genetic factors, what we really need to be doing is supporting women to make healthy lifestyle choices before and during pregnancy," said Claire.

"For women who have already been identified as carriers of a particular polymorphism, perhaps we can give them some good news - that they can probably reduce their risk of poor pregnancy outcomes by eating properly and maintaining a healthy body weight."

Claire would also like to continue this line of work into the future to ensure that women at high risk of suffering preeclampsia or delivering small and premature babies can be identified at the start of, or even before, pregnancy.

"It would be so valuable to be able to track women who are at highest risk, and offer them lifestyle support and tailor their antenatal care," she said.

More broadly, Claire also has an interest in the potential that pregnancy offers as a brief window into the future health of women.

"How a woman copes physiologically with pregnancy can be predictive of her lifetime health, for example in terms of risk of high blood pressure, diabetes and cardiovascular disease," says Claire.

"To me, we've got this opportunity in reproduction. Perhaps we could be using information gained through monitoring reproductive health to inform other health decisions. It's an area which I'm interested in exploring further."



Professor Claire Roberts, Co-Director of the Placental Development Group

Stressed-out oocytes could explain reduced fertility in obesity

High rates of obesity in Australia and other societies are creating an increasing burden on the public health system.

Fertility is just one area of health that is negatively impacted by obesity - with overweight women often experiencing delays in conception as well as problems in pregnancy, birth and health of their children. As head of the Robinson Institute's Ovarian Cell Biology Group, Dr Rebecca Robker is working to identify the molecular mechanisms through which obesity impacts on ovarian function and oocyte quality. In 2012, she discovered that obesity could reduce fertility through creating stress in oocytes.

Obesity is a global epidemic, with rates in Australia amongst the highest in the world. Identified as a major contributing factor in many acquired diseases, obesity is now also known to cause problems with reproduction. In women, obesity is associated with reduced fertility, altered embryo growth, relatively poor birth outcomes and elevated risk of obesity in offspring. Such changes are thought to stem primarily from metabolic disruption of oocytes, although the mechanisms through which this occurs remain unknown.

Leader of the Robinson Institute's Ovarian Cell Biology Group, Rebecca Robker is interested in unraveling exactly what goes wrong in the ovaries of obese women.

Her research background places her in the perfect position to do so.

"I did my PhD work in the USA on ovarian folliculogenesis and ovulation, and then did a post-doc studying immune cell infiltration into adipose tissue during obesity," explained Rebecca.

"When I moved to Adelaide, I heard a lot from Robinson Institute Director Professor Rob Norman about how obesity was associated with female infertility and conditions such as polycystic ovary syndrome. Because of my expertise in both areas, Rob and I began working together to look at the biological mechanisms." Rebecca was awarded an NHMRC Project Grant to begin to address this big question.

During 2012 Rebecca along with post-doctoral colleague Dr Linda Wu managed to identify a key problem in oocytes maturing in an obese environment. In a paper published in the journal *Molecular Endocrinology*, Rebecca and Linda showed that in mouse oocytes, in vitro culture with the obesity-induced molecule palmitic acid causes an intracellular stress response in the oocyte. The stress response was measured by looking at two key intracellular organelles required for the normal development of competent oocytes: the endoplasmic reticulum (which produces proteins) and the mitochondria (which generates energy).

"We found that culturing oocytes with palmitic acid interfered with the production of an important extracellular ovarian protein by the endoplasmic reticulum and reduced the function of mitochondria. This led to reduced in vitro fertilisation rates, and slower development to the blastocyst stage of embryogenesis," said Rebecca.

Rebecca believes the stress response could reduce fertility by preventing the production of key proteins required for normal oocyte development and ovulation, and reducing the capacity of the egg to meet the energy demands of maturation and fertilisation. It's a mechanism that might also be valid for humans.

"We think that this could also be happening in women, with obesity resulting in higher levels of molecules such as palmitic acid in follicular fluid which then creates a stress response in oocytes," said Rebecca.

Rebecca is already looking at the human angle by working with infertility specialists Louise Hull and Michael Barry, as well as Prof Norman, at the Fertility SA clinic.

"We've already started collecting ovarian follicular fluid, cells that are discarded during the IVF process and eggs that fail to fertilise," said Rebecca.

"We plan to look at the effect of obesity on the amount of fat and related molecules in the follicular fluid and eggs, as well as endoplasmic reticulum stress markers in the oocytes and other cells."

Rebecca and her colleagues are also very interested in identifying potential therapies that can act through these pathways.

"We are looking very closely at candidate drugs that can be used to reduce obesity-induced stress in oocytes. They could be used in women as a pharmaceutical to improve embryo health or in the laboratory as part of the IVF process," said Rebecca.

However, she emphasised the critical role that prevention can play.

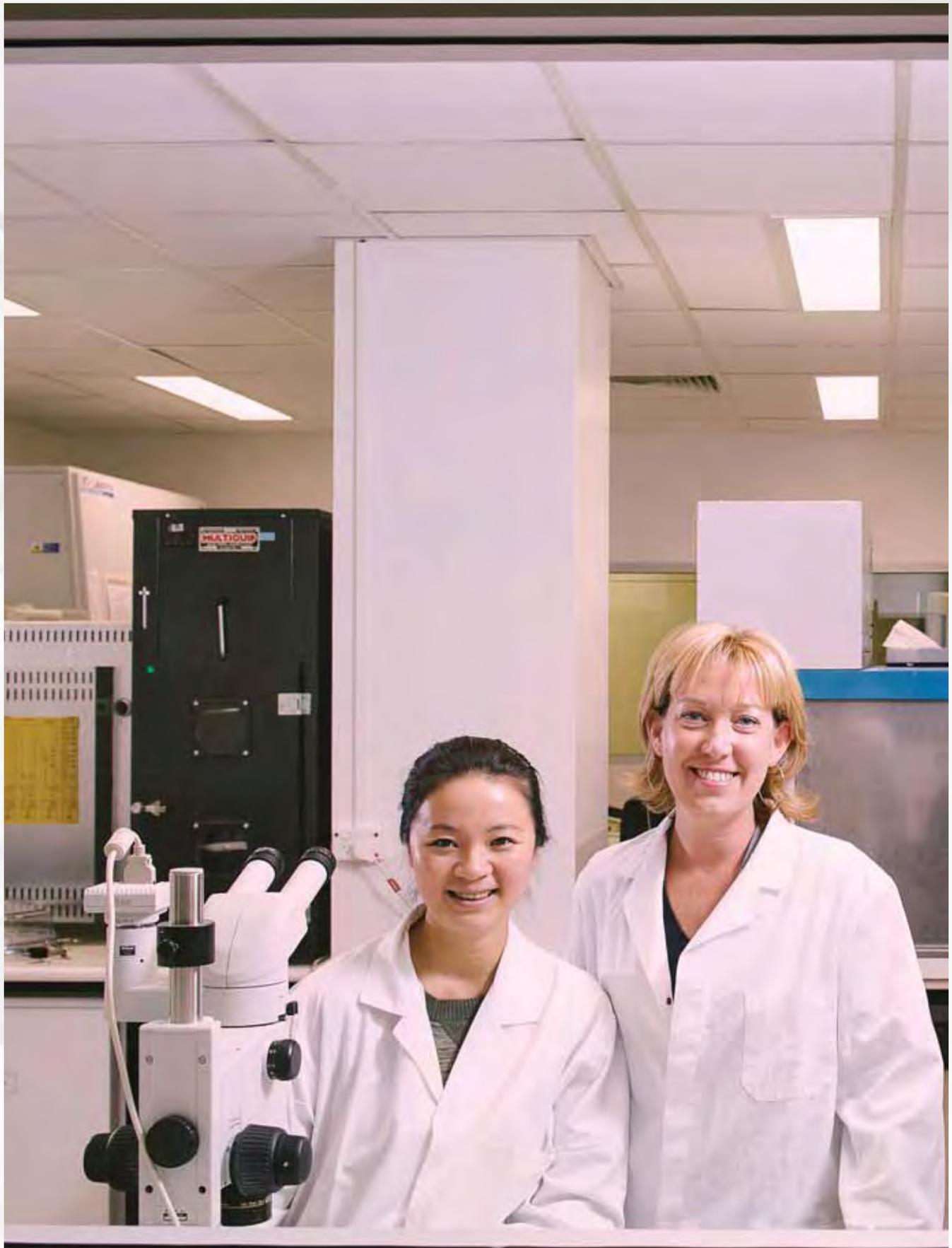
"Most importantly, we are looking at lifestyle modifications that can achieve the same outcome. Demonstrating that obesity is harmful to a woman's oocytes and has lasting consequences on the development of her future children can be a powerful health message. It should be yet another reason that young women are strongly encouraged to maintain a healthy body weight," said Rebecca.

She is passionate about continuing the work further.

"In combination with other data, this work shows that oocytes are exquisitely sensitive to their nutritional environment. That poor nutrition can alter the way that the embryo forms is amazing and at the same time a little bit terrifying," said Rebecca.

"I believe it's critical to continue this line of research to provide data for evidence-based health policies and pre-conception advice for women."

Rebecca has successfully obtained a Women's and Children's Hospital Foundation Research Grant and a Channel 7 Children's Research Foundation Grant to continue this work in the short term.



Left: Dr Linda Wu, Postdoctoral Researcher. Right: Dr Rebecca Robker, Head of the Ovarian Cell Biology Group

Male obesity reduces fertility and compromises the health of future generations

Obesity is one of the greatest public health challenges faced by Australia and many other nations.

The negative impact of high body mass can be seen in many physiological systems, including reproduction in women. At the Robinson Institute, Dr Michelle Lane's Gamete and Embryo Biology Group is building clinical and scientific evidence showing that obesity in fathers also has detrimental effects on fertility and offspring health.

Across the world, 400 million adults are classified as obese. Women who are very overweight experience substantial problems with fertility, including reduced probability of conceiving, increased risk of early and recurrent miscarriage and poorer outcomes with assisted reproductive technologies such as IVF.

It is now clear that obesity in men also diminishes fertility. In 2012, Michelle and colleagues published two unique studies that substantially advance knowledge of the underlying pathways. Research Fellow Tod Fullston showed for the first time an intergenerational effect of paternal obesity on gamete health. Male mice that became obese through eating a high fat diet showed higher rates of abnormal and damaged sperm.



Furthermore, male and female progeny of overweight males, as well as their progeny (2nd generation), all showed higher rates of compromised gamete health - with physiologically abnormal sperm and eggs reported to varying degrees in each generation. This is the first observation of paternal transmission of reduced reproductive health to future generations.

The good news is that in another first, PhD candidate Nicole Palmer showed that abnormal sperm motility and physiology resulting from obesity are reversible. Overweight male mice subjected to diet or exercise interventions to repair metabolic health showed a 'rescue' effect in measures of sperm health including motility, morphology, DNA damage and binding capability.

Together, these 2012 studies support and extend Michelle's hypothesis that male obesity reprograms reproductive potential through damaging sperm.

The move to investigate male fertility has been a relatively recent one for Michelle. With rates of obesity in men of reproductive age nearly tripling since the 1970s, and anecdotal evidence from fertility clinics linking poor reproductive outcomes with obesity - not just in mothers but also fathers - it made sense.

"We've been working in this area for around four years," explains Michelle.

"We started by doing epidemiological analysis of data from humans, looking at the association between male obesity and sperm health, rates of pregnancy and embryo development".

Michelle's research did indeed find that male obesity in humans was strongly linked with poor sperm health, lowered pregnancy rates and compromised embryo development. She then progressed to looking at mechanisms, exploring the relationships seen in the human epidemiological studies in a mouse model of obesity. It was a move that paid off.

"Our work in mice recapitulated what we had seen in the human data," said Michelle.

"We found male obesity in mice resulted in reduced ability of sperm to achieve fertilisation, impaired embryo development and reduced live birth rates".

"It made sense to extend these findings by looking at the offspring, and whether the changes were reversible, as described in the most recent of our publications".

Future work will address the metabolic impact of male obesity across generations, as well as whether diet and exercise interventions improve not only paternal sperm parameters, but also embryonic and fetal development in the next and subsequent generations.

Michelle would also like to explore the interaction between male and female obesity and its impact on multigenerational health.

Her group is uniquely-placed to do these additional studies, with group members having expertise in working with gametes in both sexes.

"There are very few groups that have expertise across both male and female gametes; we do both," she said.

Michelle's group is also unique in that it includes a comprehensive translational program, whereby research results can be used to inform clinical practice where appropriate.

"In conjunction with data from other groups, our findings have already influenced on clinical practice in Australian IVF clinics," said Michelle.

"Now men are included in the conversations about fertility and lifestyle, whereas it used to just be women. This has been really well-accepted by the potential fathers to be. Often males can tend to feel a bit isolated in conversations in IVF clinics."



Dr Michelle Lane, Head of the Gamete and Embryo Biology Group

Strengthening health services for Aboriginal women and children

Pregnancy and childbirth, like many other aspects of health, pose additional challenges for Aboriginal women.



The South Australian Aboriginal Family Birthing Program offers care to Aboriginal women during pregnancy, birth and the postnatal period. In 2012, Philippa Middleton and her colleagues at the Robinson Institute's Indigenous Maternal Perinatal Health Group secured a grant from the Women's and Children's Health Network to evaluate this program. Once finalised the report will form an important evidence base to create effective strategies to improve the health of Aboriginal women and their babies.

Pregnancy and childbirth carry elevated risks for Australian Aboriginal and Torres Strait Islander women and their babies compared to other Australian women.

Aboriginal women are between two to five times more likely to die in childbirth than non-Aboriginal women, and two to three times more likely to have a low birthweight infant.

In turn, babies with a low birthweight are more likely to develop chronic health problems in adult life. However, recent data suggests that in some Australian states, including South Australia, it is likely infant mortality rates may be falling.

To better meet the needs of Aboriginal women in South Australia, the SA Aboriginal Family Birthing Program was initiated across country areas and in urban Adelaide. The program enables Aboriginal women to be cared for during pregnancy, labour, birth and the postnatal period by Aboriginal Maternal and Infant Care (AMIC) workers in partnership with midwives, obstetricians and general practitioners.

In 2012 the Robinson Institute's Indigenous Maternal Perinatal Health Group successfully secured a grant from the Women's and Children's Health Network to evaluate the success of this program. The project is being conducted in collaboration with the Murdoch Children's Research Institute and Pangula Mannamurra Incorporated.

"We're thrilled to be a part of this very important project and delighted to be working closely with Associate Professor Stephanie Brown from the Murdoch to conduct this work," said Group leader Philippa Middleton.

Stephanie Brown is a prominent researcher in the field of Aboriginal perinatal health, and heads the NHMRC-funded Aboriginal

Families Study. Together, the SA Aboriginal Family Birthing Program and the Aboriginal Families Study are focused on the relationship between access to better quality care and more appropriate care for Aboriginal women and children and their health.

As explained by Stephanie,

"The Aboriginal Families Study aims to ensure that the voices of Aboriginal women and their families are accessible to policymakers, health service managers and service providers as evidence to inform ongoing efforts to strengthen services."

With national success already evident in Stephanie's work, in South Australia the signs are also good. Early findings from evaluating the SA Aboriginal Families Study indicate that appropriate perinatal care is improving health and social outcomes for Aboriginal families in this state.

In early 2014, Philippa and her colleagues will provide a report to the Women's and Children's Health Network, including recommendations for the ongoing operation and sustainability of the Program.

"The evaluation report will detail where the Program is working well in meeting its stated intent, and provide recommendations to strengthen activities where further work is needed," said Philippa.

"Together with data from the Aboriginal Families Study, the results will generate an evidence base to improve the design and implementation of health initiatives and services for Aboriginal women during pregnancy and around the time of delivery."



Ms Philippa Middleton, Head of the Indigenous Maternal Perinatal Health Group

Full term pregnancies – how long is too long?

It would seem reasonable to assume that the longer a fetus remains inside the uterus, the better off the baby will be. However the risk of poor health outcomes in babies and mothers can in fact increase when pregnancies continue beyond term.

One of the key decisions to be made by clinicians managing pregnancy is when to induce birth. The Robinson Institute's Australian Research Centre for Health of Women and Babies (ARCH) is committed to generating and reviewing scientific and clinical evidence relating to the care of women and babies. In 2012 the Centre published two seminal papers relating to best timing of birth for prolonged pregnancies and for twin pregnancies.

Under ideal conditions, the end-point of pregnancy – referred to as 'term' – occurs when the fetus reaches its full intrauterine growth potential and is at peak biological readiness for life outside the womb.

Term is considered to be approximately 40 weeks, with a normal range between 37 and 42 weeks. Late births are thought to carry an increased chance of complications for both baby and mother. However, because in Australia and other 'Western' societies the incidence of most poor birth outcomes is low, it can be hard to measure and compare occurrences on a population level. As a result, a key management issue for obstetric clinicians is to weigh up the risks of inducing birth against those associated with letting pregnancies progress beyond term.

Members of ARCH are committed to generating an evidence-base to guide best practice birth management, including for extended pregnancies.

"What to do in prolonged pregnancy is controversial as this situation can result in babies dying," said ARCH Executive Director Philippa Middleton.

During 2012, research groups within the Centre looked at birth timing and pregnancy outcomes in both singleton and twin pregnancies and published two key papers addressing this topic.

To investigate timing of delivery in singleton pregnancies, Philippa along with Clinical Director Professor Caroline Crowther and ARCH member Emer Heatley worked with a colleague at the World Health Organization, Dr Metin Gulmezoglu. The researchers evaluated results from 22 trials (9,383 women) to update the internationally-recognised Cochrane review article 'Induction of labour for improving birth outcomes for women at or beyond term'. The review compared birth outcomes in pregnancies where labour was induced at 37-42 weeks with birth outcomes in pregnancies that were expectantly managed (i.e. allowed to progress until labour started spontaneously). Although fetal deaths were very rare overall, the pooled data showed that induction of labour at or beyond term prevents children dying. Babies born following induction were approximately 30% less likely to die than those delivered after expectant management. In terms of absolute numbers, one baby death occurred in the induced pregnancy groups, and 13 deaths occurred in the expectant groups.

"Clearly, the data show that induction of labour can save babies' lives," said Philippa.

"Since publication, we're pleased that this research has already had an impact in maternity hospitals," she added.

"The data has been highly cited and used to formulate and update policies and guidelines on managing prolonged pregnancies around the world."

In addition to singletons, ARCH Research Leader Professor Jodie Dodd was interested in gathering data relating to the best timing of delivery in twin pregnancies. When two babies compete for resources in the womb, growth can become restricted late in pregnancy due to limitations of physical space and the diminishing capacity of the placenta (or placentas) to deliver nutrients. Beyond the 38 week mark has historically been considered as 'post-term' in twin pregnancies, although limited evidence suggested that 37 weeks might be a better end-point.

To measure the impact of delivery timing on twin health, Jodie conducted a randomised controlled trial. A total of 235 women pregnant with twins consented to be randomly allocated to deliver at 37 weeks (the Elective Birth Group) or according to standard delivery procedures (the Standard Care Group – most of whom delivered around 38 weeks or later). A composite measure was used as an indicator of serious poor health outcomes in the newborn babies: this factored in birth weight, adverse events at birth, immaturity and infection.

The results showed that while approximately 12% of twin babies in the Standard Care Group experienced a serious poor health outcome, only about 5% of those in the Elective Care Group had a similar outcome. This means the risk of a serious poor health outcome



Ms Philippa Middleton, ARCH Executive Director



Professor Jodie Dodd, Head of the Multiple Pregnancy Group

after delivery at 37 weeks was reduced by more than half compared to the Standard Care Group. The difference was attributed mainly to a greater likelihood for twin babies delivered at 38 weeks or later to have a very low birth weight (in the lowest 3% of all babies born at that gestational age).

Importantly, the health benefits of delivering twins at 37 weeks in this study occurred without any increase in complications associated with infant immaturity and with no detrimental effect on health of the new mothers in the perinatal period.

Jodie's results are also changing clinical practice. "It's filtering out," says Jodie. "We've had a lot of interest and comments from obstetric centres, and a number of these have already changed their twin delivery management practices."

The results of this study will be incorporated into the Perinatal Practice Guideline, the key policy document which guides the delivery of babies in South Australian hospitals and other centres.

"The Perinatal Practice Guideline is available to all maternity centres across the state. It is considered the standard of care to which we are expected to adhere. A lot of hospitals outside the state also model their birthing practices on this guideline," says Jodie.

Jodie's next task is to use the results of her study to update the Cochrane summary relating to this area of obstetrics: 'Elective delivery of women with a twin pregnancy from 37 weeks' gestation'.

Together, the two publications show that managed induction of labour in singleton and twin pregnancy can offer health benefits for infants. Moving forward, Philippa and Jodie along with their colleagues at ARCH will continue their commitment to conduct, promote and support the preparation and updating of high quality trials and systematic reviews of the evidence on questions of relevance to women and babies in Australia, regionally in South East Asia, and internationally.

“...the pooled data showed that induction of labour at or beyond term prevents children dying”

Safer blood transfusions for preterm babies

Blood transfusions are one of the most common medical treatments required by preterm infants. Although the procedure undoubtedly saves many lives, emerging evidence suggests damage to the baby's developing organ systems may be an associated risk.

Associate Professor Michael Stark from the Robinson Institute's Neonatal Medicine Group is interested in determining why the potential side effects of blood transfusions occur. In 2012 he published the first evidence that receiving blood products triggers a surge in levels of inflammatory molecules in preterm infants. Michael recommends that more research is urgently required to better manage and ideally prevent this response.

Every year in Australia about 8% of babies are born before 37 weeks of pregnancy, and classified as preterm. Many of these infants require intensive medical support to survive. Very early babies often need red blood cell transfusions due to anaemia or following blood loss. Although this procedure undoubtedly saves many lives, it can also initiate inflammatory processes. What leads to this development is not well understood.

Michael Stark, Neonatologist and researcher in the Robinson Institute's Neonatal Medicine Group, is working to understand what triggers the effects of blood transfusions in preterm infants. In 2012 he published a study that revealed transfusion elicits a cascade of inflammatory changes.

"Within two to four hours of preterm

babies receiving a blood transfusion, we have seen elevated levels of molecules known as cytokines and chemokines that in turn stimulate further inflammatory responses in the body," Michael says.

Michael believes that once such molecules are triggered in the hours following a blood transfusion, they act within the child's body to initiate high levels of inflammation that results in damage to blood vessels and tissue structures. Such events contribute to the development of significant conditions that complicate very preterm birth, such as bronchopulmonary dysplasia in the lungs and necrotising enterocolitis in the gut.

Although Michael has not yet determined exactly which components of blood transfusion trigger the inflammation, he has a theory.

"We believe that the bioactive components of packed red blood cell transfusions are initiating or amplifying these inflammatory processes in the body," he suggests.

Possibilities include microparticles, iron or fatty molecules known as phospholipids that accumulate over time. More work is required to explore this further and determine how best to address the clinical challenges posed by blood transfusion in preterm babies.

"More research is now needed to determine exactly how this response is triggered, and how we might be able to prevent it," said Michael.

"We hope that by better understanding how the body responds to the blood, we can make improvements to blood transfusions that will reduce the likelihood of inflammatory responses. In this way, the patient will benefit from a life-saving procedure and also experience fewer complications."

Despite the need for ongoing research, Michael emphasises the critical role that transfusions still play in the management of preterm infants.

"Blood transfusions are a safe and life-saving medical procedure - they are an important part of modern-day medical care," he said.

"We'd just like to be able to prevent and manage their side effects a little better."

Michael's study was conducted at the Women and Children's Hospital in Adelaide, and included infants born before 28 weeks of gestation that were clinically-indicated to require blood transfusion. The research was undertaken in collaboration with the Australian Red Cross Blood Service and supported by the Australian & New Zealand Society of Blood Transfusion Ltd and The Robinson Institute.

“Very early babies often need red blood cell transfusions due to being anaemic or following blood loss”



Associate Professor Michael Stark, Neonatologist and Researcher with Rebecca Lawson-Cook and daughter Eliza Lawson

Preterm birth affects learning and memory abilities

It has long been known that children born preterm are at increased risk of developmental problems, but to date, the tools to identify and treat affected individuals have been of limited effectiveness.

Dr Julia Pitcher and Associate Professor Michael Ridding of the Robinson Institute's Neuromotor Plasticity and Development (NeuroPAD) Group are interested in how the brain responds to lifetime experiences by changing connections between brain cells, a phenomenon known as neuroplasticity. Their recent work shows that teenagers who had been born preterm showed relatively low brain plasticity in association with abnormally low levels of salivary cortisol. The data sheds light on the mechanism behind developmental problems with memory and learning due to preterm delivery, and may open up new avenues for diagnosis and treatment.

The human brain shows remarkable flexibility and resilience in the way it responds to the world. Neuroscientists use the term 'plasticity' to describe the lifelong ability of the brain to change its structure and function in response to experience and incoming stimuli from the environment. The high degree of plasticity in children's brains is clearly evident in the enormous changes that take place in their development during infancy, early childhood and primary and secondary schooling.

In 2012 Julia and Michael published data promoting the first evidence that being born preterm – before 37 weeks of pregnancy – may reduce the brain's ability to undergo plastic change. The studies, performed by Honours student Alysha Riley, involved comparing brain plasticity in three groups of subjects: adolescents born preterm, adolescents born at term and adults born at term. The work involved use of a non-invasive magnetic brain stimulation technique to measure neuroplasticity in the study subjects.

"Teenagers born preterm clearly showed reduced neuroplasticity in response to brain stimulation," Julia said.

"Surprisingly, even very modest preterm birth was associated with a reduced brain response. On the other hand, term-born teenagers were highly 'plastic' compared with adults and the preterm teens."

These days, infants born well before 37 weeks of gestation can be supported to survive thanks to medical interventions. However this new data suggests that aspects of brain development critical for normal childhood neuroplasticity take place during the final weeks and days of pregnancy.

"The growth of the brain is rapid between 20 and 37 weeks gestation, and being born even mildly preterm appears to subtly but significantly alter brain microstructure, neural connectivity and neurochemistry," said Julia.

This novel research is opening up exciting pathways to approaching an old problem. Researchers, doctors, parents and educators have known for some time that children born preterm often have difficulties with learning, memory and motor development. However, because the problems are often subtle and occur in the absence of any detectable brain injury, interventions to help these children have not been very successful.

To further address this aspect of the problem and to investigate possible mechanisms that may be involved, Julia and Michael looked at levels of the hormone cortisol in their study subjects.

"Preterm teens had low levels of cortisol in their saliva, which was highly predictive of the reduced brain plasticity we observed," said Julia.

Cortisol is often described as a stress hormone, but the Adelaide researchers have previously shown it also has a key role in regulating brain plasticity. Cortisol levels

can be therapeutically manipulated and this could offer therapeutic potential for preterm children.

"Cortisol plays a critical role in learning, the consolidation of new knowledge into memory and the later retrieval of those memories. This might be important for the development of a possible therapy to overcome the neuroplasticity problem," she said.

Published in the prestigious *Journal of Neuroscience*, Julia and Michael's data attracted national and international attention. For the first time it showed clear physiological reasons why preterm children might have difficulties with learning and memory, and raised new possibilities for the development of targeted interventions for them.

The team is now conducting further research to more fully elucidate the role of cortisol in modulating brain development and plasticity, in particular whether cortisol affects specific types of learning and memory more than others.

From a prevention point of view, the research also adds to the already substantial body of evidence emphasising the need to support women to carry pregnancies to at least 37 weeks whenever possible.

"Even one extra week of pregnancy could make a huge difference to the future brain development of that child," said Julia.

“ Even one extra week of pregnancy could make a huge difference to the future brain development of that child ”



Dr Julia Pitcher, Co-Director NeuroPAD, Dr Luke Schneider, Postdoctoral Researcher NeuroPAD with patient

Australia's first dedicated asthma service for pregnant women

Women's bodies go through many biological changes when pregnant, and not just in the reproductive organs. Lung function is different during pregnancy: women who normally experience asthma may have it worsen, while others may experience asthma for the first time when pregnant.

As head of the Robinson Institute's Pregnancy and Development Group, Associate Professor Vicki Clifton is concerned about the impact that under-diagnosed and poorly treated maternal asthma is having on fetal health, including an increased incidence of stillbirth. To help combat this, in 2012 Vicki announced the launch of Australia's first dedicated asthma service for pregnant women.

Being pregnant places many demands on a woman's body. Extra weight along with expanded blood volume and higher metabolic rate all contribute to the physiological burden of pregnancy. Lung function also changes during pregnancy, with conditions such as asthma often worsening and causing respiratory difficulties. It is now clear that in addition to troubling the woman, increased incidence and severity of asthma during pregnancy can create serious health issues for her child, including growth restriction, preterm delivery and even stillbirth.

Associate Professor Vicki Clifton, head of the Robinson Institute's Pregnancy and Development Group, is committed to preventing the negative impacts of asthma during pregnancy. In 2012 she announced the launch of Australia's first dedicated asthma service for pregnant women.

"Unfortunately, asthma has been poorly treated during pregnancy for many years," said Vicki.

"Currently there is no dedicated asthma service for pregnant women in Australia, and government funding is not forthcoming to support a trial to determine the cost effectiveness and clinical effectiveness of such a service."

"We will run a trial service in 2013 on a limited budget, because we believe this is an extremely important initiative to change clinical practice and help a large proportion of pregnant women in Australia," she said.

Vicki's drive to initiate the trial service stems from her extensive research experience, and her knowledge of the statistics relating to asthma during pregnancy. According to data collected by SA Health, asthma complicates up to 16% of pregnancies in South Australia, and is a significant contributing factor in up to one fifth of preterm births, stillbirths and delivery of growth-restricted fetuses in this state. Asthma is also associated with other serious complications of pregnancy, such as preeclampsia, gestational diabetes, haemorrhage and congenital abnormalities.

Despite these statistics, less than half of the cases of asthma in pregnancy are currently identified. To complicate the picture further, even if aware of their condition, women show some reluctance to use their normal asthma medications when pregnant.

"Asthma is being under-reported during antenatal visits and is therefore under-treated," said Vicki.

"There is also a misconception with pregnant women that their asthma medication may harm the baby. In fact, the asthma is much more likely to be harmful than the preventive medicine," she says.

"There needs to be more awareness around the management of asthma during pregnancy and the importance of taking preventive medication while pregnant."

In the past, Vicki has conducted a number of research projects on the impact of asthma on mothers and their babies, and in 2013 she will take up a new five-year research fellowship focussed on this work,

funded by the National Health and Medical Research Council (NHMRC).

"We now have more information than ever before about how and why asthma worsens during pregnancy, and why it can have such a detrimental effect on the baby, but much more research needs to be done," she says.

In addition to conducting further research, Vicki emphasises the need to see improvements in clinical practice.

"By introducing a dedicated asthma service, we hope to raise awareness of the problems experienced by mothers and their unborn babies from asthma, and provide treatment and advice," she explained.

"Ultimately, with the right care and management, our aim is to reduce the number of preterm births, stillbirths, and growth-restricted fetuses that are directly affected by asthma."

Also a member of Vicki's Pregnancy and Development Group is Dr Annette Osei-Kumah, who in 2012 was awarded the inaugural Florey Early Career Northern Health Research Fellowship. The fellowship allowed Annette to conduct a two-year research project at the Lyell McEwin Hospital, helping pregnant women in the northern suburbs of Adelaide manage their asthma and reduce the health risks for their unborn child.

“Unfortunately, asthma has been poorly treated during pregnancy for many years”



Associate Professor Vicki Clifton, Head of the Pregnancy and Development Group

Making strides in the fight against Meningococcal B disease

Meningococcal disease is the leading infectious cause of death in children and adolescents, and can leave families reeling with its rapid and devastating impact.

The Robinson Institute's Vaccinology and Immunology Research Trials Unit has contributed to several important studies investigating the safety and efficacy of vaccines against the most common and virulent cause of meningococcal disease, Strain B Meningococcal bacteria.

Neisseria meningitidis, or Meningococcus bacteria, is a frequent and normally unnoticed inhabitant of the human nasopharynx. Meningococcal disease occurs when the bacteria enter the bloodstream, proliferate rapidly and lead to inflammation of peripheral blood vessels and the meningeal lining of the brain, resulting in septicaemia and meningitis. In Australia, 10-15% of children and adolescents who acquire the disease lose their lives. Even if they do survive, there is a 40% chance of long term disability due to limb ischaemia requiring amputation, hearing loss, neurological damage or skin scarring.

Australia does not currently have a licensed vaccine to immunise against Strain B Meningococcus, which causes 80% of all cases of meningococcal disease. Licensed vaccines against the less prevalent Strain C Meningococcus have been very successful in substantially reducing cases due to Strain C disease, but don't offer cross protection against Strain B.

In 2011, there were 22 cases of meningococcal disease in South Australia: 17 of those cases were caused by Strain B Meningococcus.

During 2012, the Vaccinology and Immunology Research Trials Unit (VIRTU) published five studies addressing safety and efficacy of vaccines targeting Strain B Meningococcus. The work represents a first step in the drive towards a new vaccine being licensed for use in Australia.

Unit Director Associate Professor Helen Marshall explained, "Having a vaccine to prevent Strain B Meningococcal infections would be of enormous value. Our recent studies show we are rapidly progressing towards this point."

A good Strain B Meningococcal vaccine needs to be well-tolerated in recipients of all ages, offer immune protection against all sequelae following infection, and be effective against the different subtypes of the B strain. It must also generate antibodies that persist and provide long-term protection.

The studies conducted so far by Helen and her colleagues looked at the safety and immunogenicity – the capacity of the vaccine to generate effective immune responses – of a Meningococcal Strain B vaccine in toddlers, children, adolescents

“Australia does not currently have a licensed vaccine to immunise against Strain B Meningococcus”

and adults. The vaccine was found to be well-tolerated and immunogenic in all age groups, suggesting it may be a good candidate for protection against invasive Strain B Meningococcal disease.

"While these studies are promising, we need to complete the final studies before the vaccine can be reviewed for licensing by the regulatory authorities," said Helen.

"In addition, the ideal immunisation schedule to provide long term protection against invasive meningococcal disease is yet to be established. Monitoring long term persistence of antibodies post immunisation will inform timing of future booster vaccinations to provide the best protection in at risk age groups and in children with underlying immunosuppressive conditions."

"We also need to refine immunisation protocols for target age-groups," added Helen.

"Because most Strain B Meningococcal cases occur in children less than 5 years of age, the ideal time point for a meningococcal B vaccine program would be an infant program commencing at 2 months of age. However a school program would also be valuable given there is a second peak of meningococcal disease in adolescence."

Helen and her colleagues at VIRTU are already conducting additional studies aimed at addressing these issues, and hope to contribute to the evidence base supporting licensing of a vaccine against Strain B Meningococcal in Australia.





Associate Professor Helen Marshall, Director of the Vaccinology and Immunology Research Trials with baby Leo

A new angle for fighting infection and preventing harmful side effects

We've all experienced the debilitating symptoms of infection. Shaking, shivering, bone aches and high fevers are the side effects of small hormone-like molecules produced by our immune system while fighting disease.

When high levels of a particular molecule known as TNF are induced during some infections, side effects can include extreme pain, disability and even death. Head of the Robinson Institute's Developmental Genetic Immunology Group, Professor Tony Ferrante has spent his 30-year career investigating how to offer therapeutic tools relating to TNF and its wanted and unwanted actions. A serendipitous discovery during 2012 may have taken him one step closer.

Tumour necrosis factor, or TNF, is a small hormone-like molecule produced by cells of the immune system in response to infection and inflammation. This protein has an incredibly strong potency within the human body. Whilst some of this activity aides infection recovery, other aspects are very damaging to health. The negative effects of TNF include suppressed appetite, wasting of body tissues, fever, shock-like syndromes and the classic symptoms of inflammation: heat, swelling, redness, pain and loss of function.

The 'dark' and 'light' sides of TNF's activities have plagued immunologist Tony Ferrante throughout his 30-year career working in diagnostics and inflammatory conditions. As head of the Robinson Institute's Developmental Genetic Immunology Group, Tony knows how critical TNF can be in resolving infections, but has also seen the side effects.

"The old adage 'you need the illness to fight the infection' certainly holds true in many cases," said Tony.

"But TNF often takes it one step too far. Yes, it's a molecule which is critical to fight infections, but it can also tip the balance over into inflammatory syndromes which are highly dangerous and end up being a separate problem to the actual infection."

"Malaria is a good example, where the excessive production of TNF helps to fight infection but also leads to very high fever, inflammation and lysis of red blood cells, which can eventually kill the patient independently of the actual parasite burden," added Tony.

TNF acts on several cell types in a very targeted manner, binding to specific TNF-receptors that trigger a cascade of other effects through the activation of intracellular signaling pathways.

The two contrasting arms of TNF have limited the development of any effective targeted clinical treatments relating to its actions. Blocking the unwanted effects through preventing receptor binding also prevents the wanted effects being activated. From the other angle, trying to help patients clear infectious pathogens by treating with TNF is not possible due to the risk of triggering dangerous side effects.

"It's a dual-edged sword, and a source of great frustration for scientists and clinicians," said Tony.

Hence Tony was delighted when during 2012 some serendipitous research opened up a new possibility of solving this dilemma.

Scientists in Tony's lab made several fragments of the TNF-receptor, and tested their capacity to bind to TNF. One of these fragments had special properties that attracted their attention.

"We found that this particular fragment bound to a key region on free-floating TNF. Although the fragment-TNF complex could then still bind to TNF receptors in cell membranes, it somehow changed the activation pathways that were induced," said Tony.

Tony and his colleagues tested the impact of the fragment on disease outcomes, measure of inflammation and intracellular

signaling in mice.

"We think that this fragment blocks the capacity of TNF to activate an intracellular signal known as p38, whilst maintaining the activation of the other important pathways," explained Tony.

The p38 signal is associated with amplification of inflammatory and cell death biological responses in cells.

The possibility that the fragment-TNF complex may trigger only the wanted biological effects of TNF, and not the dangerous side effects, could have applications in therapy. For example, treating infections with the fragment could lead to maintenance of disease-clearing immune activity whilst blocking excessive, symptomatic inflammation.

For now though, it's still early days.

With initial grant support for this work from Australia's NHMRC, Tony has now applied for additional funding to extend the work "to explore pharmacokinetics and looking at the chemical and physical nature of the fragment-TNF complex," said Tony.

"This line of research could address a problem that has vexed us for many years."

"The possibility that it could lead to the development of safe and selective treatments not only for chronic inflammatory condition but also inflammation associated with infection is very exciting," he smiled.

“ Tumour necrosis factor, or TNF, is a small hormone-like molecule produced by cells of the immune system ”



Professor Tony Ferrante, Head of the Developmental Genetic Immunology Group



Commercial Development

Advancing reproductive and paediatric health relies on creating new technologies, developing commercial innovations and fostering successful partnerships.

In 2012 the Robinson Institute generated more than \$600,000 in contract research and consulting income working with a variety of industry partners. Members also made a number of innovative research discoveries which have the potential to transform future medical practice.

Diagnostic for endometriosis

The Endometriosis Research Group at the Robinson Institute has identified biomarkers (microRNAs) in human blood that are indicative of endometriosis. To support further development of this discovery, Bio Innovation SA awarded Adelaide Research & Innovation a \$97,000 Commercial Development Initiative grant. The project currently seeks to clinically validate the identified blood-based biomarkers in order to produce a prototype blood test for endometriosis, which will ultimately reduce the need for invasive surgical diagnosis of this common disease. The

proposed endometriosis diagnostic is being developed by Dr Louise Hull, Professor Sarah Robertson and Dr Vicki Nisenblat, in collaboration with Associate Professor Cristin Print from the University of Auckland.

EmbryoGen®

EmbryoGen® is a new treatment product for miscarriage containing the cytokine Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF). Developed in collaboration with Origio A/S (Denmark), EmbryoGen® offers a novel treatment option for women undergoing in vitro fertilisation (IVF) after a history of one or more miscarriages. The scientific foundation behind the technology has been fostered by Professor Sarah Robertson, who has spent more than 20 years developing this niche approach. The key to its success is the technology's ability to closely mimic the natural environment of the uterus and support early embryo growth and firm implantation. In December 2012 EmbryoGen® was launched onto

the US market at the American Society for Reproductive Medicine, San Diego, after receiving approval from the Food and Drug Administration (FDA). In Australia, Fertility SA launched a clinical trial with the treatment, offering EmbryoGen® to support reproduction in patients who have suffered miscarriage. Approval is being sought from the Therapeutic Goods Administration to allow launch across Australia.

IVF Vet Solutions

Led by Associate Professor Jeremy Thompson, the IVF Vet Solutions business unit capitalises on the wealth of embryology expertise at the Robinson Institute to provide a range of services to the IVF market. One of the premier products of the unit is the mouse embryo assay (MEA), which is a quality assurance test for media and other products used in IVF. The unit is currently developing a suite of bovine IVF media, supported by Adelaide Research & Innovation's Commercial Accelerator Scheme. Under the development program, IVF Vet Solutions is producing and supplying research media to collaborating commercial bovine IVF providers, with the goal of validating the media suite in a commercial setting.

Mesoblast

Adelaide Research & Innovation has assigned exciting adult stem cell technology to Australian regenerative medicine giant Mesoblast in a deal which could lead to a cure for stroke sufferers. Developed by Professor Simon Koblar, the stem cell technology has shown that human stem cells derived from adult teeth to have an intrinsic ability to form brain cells and interact with the nervous system. This research has the potential to provide real benefit to those who have suffered a stroke. However, it must undergo pre-clinical and clinical trial phases before it can be rolled out to the market place. Mesoblast is currently conducting clinical trials employing the stem cell therapy for cardiovascular disease, diabetic nephropathy, osteoarthritis and cancer. Professor Koblar will act in a key advisory role across the pre-clinical trial and clinical trials.

Licensing T-Reg technology to Transbio

Associate Professor Simon Barry has discovered novel biomarkers for identifying regulatory T cells (T-reg), an important immune cell population. This discovery was licenced to Transbio, the commercial arm of the CRC for Biomarker translation, granting them the right to lead the commercialisation of this technology.

Production and supply of antibodies

Associate Professor David Kennaway has a commercial relationship with Buhmann Laboratories relating to the supply and use of melatonin antibodies. The antibodies are incorporated into kits sold by Buhmann for commercial and research needs.

Collaboration with Cook Medical

Cook Medical LLC is a large privately owned medical device company based in Bloomington, Indiana (USA). Cook makes over 30,000 medical and surgical products, and their Women's Health Division is an important global producer of IVF products. For the past 10 years, Cook has been a strong supporter of the Robinson Institute, including partnering on grants, engagement



of Associate Professor Jeremy Thompson and Robert Gilchrist as consultants and strengthening of many research projects which focussed on development of ART technologies. Cook has also supported the filing of patents related to ART technologies, and provided career development opportunities for Robinson Institute members through the Cook Medical Fellowship Program. Cook is the commercial partner on the Premier's Science Research Fund (PSRF) and Australian Research Council (ARC) Linkage Grants related to the Sensing Technologies for Advanced Reproductive Research (STARR) lab, which is a joint project between the Robinson Institute and the Institute for Photonics and Advanced Sensing (IPAS).

Clinical trials

Robinson Institute researchers are conducting sponsored clinical trials with companies such as Medpace Australia, Merck and Bayer.

New patents

Indicative of the Robinson Institute's strong culture of commercial innovation, members filed new patent applications in the following areas during 2012: swallowing disorders, endometriosis, reproductive biology and schizophrenia.

Expert Panel to the NHMRC

The National Medical Health and Research Council is Australia's peak body for supporting health and medical research. During 2012, a team from the Robinson Institute's Australian Research Centre for Health of Women and Babies (ARCH) continued to provide services to an NHMRC Panel of Providers with Expertise Relevant to the Development and Presentation of Evidence Based Health Advice. As examples, ARCH developed the National Evidence-Based Antenatal Care Guidelines and also provided expert advice to Cancer Australia in relation to the grading of clinical practice recommendations. Professor Sarah Robertson, Professor Ray Rodgers and Professor Julie Owens were appointed as Members of the NHMRC Assigner's Academy in 2012.

Exciting discovery for targeted diagnosis and treatment of schizophrenia

Despite the advances of modern medicine, schizophrenia remains a poorly understood and debilitating brain condition affecting 1% of the population.

Because the mechanisms that cause schizophrenia are unknown, diagnosis and treatment rely on non-specific clinical assessments and 'broad-brush' therapies.

Dr Quenten Schwarz conducts research as head of the Robinson Institute's Neurovascular Research Group looking at development of the brain and nervous system. During 2012, Quenten made an exciting new discovery regarding brain formation in mice, and hopes this may shed light on the search for novel alternatives for diagnosis and treatment of schizophrenia. His findings are now patent-protected for possible commercial development.

Schizophrenia is a surprisingly common brain condition that affects approximately 1 in 100 Australians following diagnosis in the teen or early adult years. For many sufferers it is a prolonged illness, involving distressing symptoms and disability resulting from disordered thinking, delusions and hallucinations as well as low motivation and changed feelings. Schizophrenia is a major cause of suicide, with 50% of sufferers attempting to end their lives.

Schizophrenia is believed to be a disorder resulting from abnormalities in the ways that nerves and organisational centres in the brain develop and form connections. Although environmental and social factors have a role in triggering the disease onset, its primary origin is almost certainly in DNA.

While there are several known genes linked to disease occurrence in humans, to date this knowledge has had little impact on diagnosis and treatment of schizophrenia. Instead, diagnosis relies on the clinical observation of so-called positive and negative symptoms once they are fully expressed in the patient. Treatment does not target the core anatomical and developmental mechanisms that lead to schizophrenia, but instead focuses on preventing psychotic manifestations through blocking activity in the brain's

central neurotransmission pathways. Thus current approaches to both diagnosis and treatment of schizophrenia are non-specific.

During 2012 Quenten Schwarz and colleagues uncovered a possible new focus for developing targeted schizophrenia diagnosis and treatment. The discovery came by working with mice deficient in a brain protein known as 14-3-3 zeta, which were available through Adelaide's Centre for Cancer Biology.

"Although we can't definitively say the 14-3-3 zeta-deficient mice have schizophrenia, we found they do have key problems in common with patients suffering from the disease," explained Quenten.

The deficient mice are hyperactive, display erratic behaviour, have a reduced capacity to learn and remember, and show disrupted sensorimotor gating.

"Impaired sensorimotor gating is one of the hallmark positive signs of schizophrenia," said Quenten.

"It relates to an incapacity to distinguish between sources of information internal and external to self."

The link between absence of the 14-3-3 zeta gene and schizophrenia-like symptoms in mice is consistent with previous studies that have reported relatively low levels of the 14-3-3 zeta protein in humans with schizophrenia.

"It's early days, but for us this has been very exciting," said Quenten.

"Even more so when we found that the 14-3-3 zeta-deficient mice also had anatomical differences in their nerves which are similar to abnormalities seen at autopsy in humans with schizophrenia."

The mice deficient in 14-3-3 zeta showed abnormal nerve fibres known as axons, and improperly formed synapses, or connections between adjacent nerve cells. Furthermore, neurons in the hippocampus region of the brain in deficient mice

are positioned abnormally. In human schizophrenia patients, the hippocampus is similarly affected.

For Quenten and his colleagues, the behavioural and anatomical evidence taken together provide proof in principle that abnormalities in the 14-3-3 zeta gene and the protein produced by it could be involved in schizophrenia.

"Schizophrenia is clearly a multi-gene disorder, but we do think the 14-3-3 zeta gene and the pathway through which it functions could have some sort of central importance in this disease," said Quenten.

Having published their first set of data in the high profile journal *Molecular Psychiatry*, Quenten's Neurovascular Research Group along with external collaborators will now conduct further research in their mouse model. In particular, they plan to focus on the possible molecular roles of 14-3-3 zeta, such as guiding nerve and brain development.

"If we understand the molecular mechanisms by which 14-3-3 zeta controls neuronal development, then maybe we can test for things that are going wrong, or modify how these processes take place," suggests Quenten.

In anticipation of these possibilities, two patents – one in diagnostics, one in therapeutics – have been filed to cover future commercial outcomes.

Quenten also plans to expand his research into clinical settings, and has forged new collaborations with this in mind.

"In Adelaide alone, we know there are over 600 patients on the highest level of treatment for schizophrenia. By developing relationships with these patients and the clinicians who manage them, we hope to be able to explore the associations between 14-3-3 zeta levels and schizophrenia in humans," said Quenten.

Quenten's research is funded by MedVet Laboratories and Australia's National Health and Medical Research Council.



Dr Quentin Schwarz, Head of the Neurovascular Research Group

A new tool to monitor swallowing disorders for better health of children and adults

Swallowing disorders, collectively referred to as dysphagia, are a hidden and potentially health threatening problem across many age groups in our society. Clinical observation of the many steps involved in swallowing is key to better management of children and adults with dysphagia.

Current technologies to conduct such evaluations are less than ideal due to subjective interpretation and exposure to X-rays. Headed by Associate Professor Taher Omari, the Robinson Institute's Gastroenterology Group has designed a new approach for clinical assessment and monitoring of dysphagia. It is felt this tool will complement current technologies and provide the first objective function measures of swallowing. The tool is now patented and in preparation for commercialisation.

The ability to swallow normally is a skill many of us take for granted. In reality, swallowing is a highly complicated act, and requires muscles and structures in our head and neck region to work together and perform a series of interdependent and coordinated phases. Each bolus of food or drink must be propelled from the mouth to the pharynx, then transitioned to the upper and lower oesophagus and finally the stomach. In addition, the airways must be protected by appropriately-timed closure of the airway and vocal cords to prevent aspiration – the entry of solids or liquids into the respiratory tract. Aspiration can lead to recurrent pneumonia, progressive lung disease, and respiratory disability or even death.

“The ability to swallow normally is a skill many of us take for granted. In reality, swallowing is a highly complicated act”

Dysphagia is a surprisingly common disorder. It occurs as part of the spectrum of feeding problems detected in approximately one third of otherwise normal children, but incidence rises sharply in those born prematurely, or with developmental disabilities and neurological conditions. For example, it has been estimated that as many as 80% of children with cerebral palsy will have dysphagia at some point.

As head of the Gastroenterology Group based at the Women's and Children's Hospital in Adelaide, Taher Omari has assessed and consulted on treatment for children with dysphagia across Australia. “Dysphagia can be distressing for many children and their parents, as it interferes with the social activity of eating and prevents adequate delivery of nutrition for normal growth and development,” he said.

“In children with congenital and neurological conditions, the consequences can be even more severe. It is very important to accurately assess swallowing ability so that appropriate clinical decisions can be made to support the child and his or her family.”

Motivated by these factors, Taher and his colleagues saw an opportunity to develop a new technique to measure dysphagia. The new method is known as AIM analysis - automated impedance manometry pressure-flow analysis. In contrast to existing approaches for evaluating dysphagia – such as observational assessment, or X-ray videofluoroscopy – AIM analysis has many advantages.

“AIM analysis is well-suited for use in children, as it is a non-radiological approach which can be performed at the bedside and gives the clinician an objective measure of swallowing function,” said Taher.

The technique involves introducing a catheter into the nose of the patient, and gently moving it back down into the throat.

During the act of swallowing, the catheter measures two aspects of performance: pressure (using manometry) and flow (using impedance). The pressure measurements give an indication of the capacity of muscles to contract and relax at appropriate time points and carry out the mechanical steps for swallowing. The flow measurements relate to movement of the bolus, such as whether its been propelled through the pharynx and oesophagus appropriately.

Not only does AIM analysis detect both pressure and flow, but it also combines the two measurements together to create a unique integrated readout.

“Combining the pressure and flow measurements together is very valuable, as we are able to obtain a picture which unites key aspects of swallowing: the physical stages in combination with the actual outcomes,” explains Taher.

“We get information about how strong a swallowing contraction is, about the pressures in the bolus, and the time relationship between the bolus being propelled and then the pharynx squeezing behind it.”

All of this information can be critical in tailoring clinical support for a child with dysphagia.

“Another advantage of this approach is that it can be fully automated. This takes away any subjective bias or variation which can arise when individuals make observational assessments of swallowing,” added Taher.

AIM analysis has now been validated in an adult population and patented, and Taher and his colleagues are in the process of negotiating a commercial license to incorporate the technology into existing assessment techniques. The method should be easily adopted by hospitals, since the catheters used for AIM analysis are already widely used in other areas of gastroenterology.

Current research at the Women's and Children's Hospital is focused on investigating children with dysphagia using AIM. In addition to children, the Gastroenterology Group anticipates that AIM analysis will have broad applications in other groups of patients, particularly the elderly.

"As people get older, their swallowing deteriorates as a normal part of ageing," explained Taher.

"If individuals then suffer a major illness, or develop a neurological problem, that can have an additive effect."

Stroke is one of the major causes of dysphagia in the older age groups, and

needs rapid and accurate assessment to be managed properly.

"From a clinical point of view, it can be critical to accurately and rapidly identify those stroke patients who are at risk of dangerous swallowing-related complications, such as aspiration," said Taher.

"Currently, when someone has a stroke a speech pathologist makes a clinical assessment of swallowing ability. The actual mechanics behind what is going wrong are not determined until an X-ray videofluoroscopy can be performed, sometimes not until days or even weeks later. We think the AIM analysis will allow

for accurate identification of dysphagia symptoms at the bedside for stroke victims who need rapid clinical attention. Results can then be interpreted by the speech pathologist and other clinicians for continued care".

Along with colleagues, Taher hopes to secure research grant funding to fine-tune AIM analysis as a predictive tool for the long-term prognosis of adult stroke victims. The technique also holds promise for use in motor neurone disease patients and those with radiotherapy-induced dysphagia following treatment for head and neck cancers.



Associate Professor Taher Omari, Head of the Gastroenterology Group

Robinson Foundation



A message from the Chair

The work that is undertaken at the Robinson Institute never ceases to amaze me. As Chair of the Robinson

Foundation Committee I am fortunate to meet some of the Institute's world-leading researchers and learn about their important work. Their passion and dedication to addressing major health burdens in our community is truly inspiring. It is for this reason we must continue to focus on raising awareness of this vital research work and the important place it has in our society.

The breadth and depth of research discoveries that emerge through the Robinson Institute are not widely recognised among the general community – and this is where we can make a real difference.

We want to inform the community about the myriad of health risks associated with fertility, conception, pregnancy, the health of babies, children and adolescents and the impact of health across generations.

We want to raise much-needed funds to support new and ongoing research to ensure our discoveries can continue and that they can be transformed into clinical care and policy for the health of all children and families, across generations and global communities.

I would like to extend my personal thanks to the Robinson Foundation Committee for their support and commitment to the Foundation and the Institute. In particular I would like to recognise the work of Ms Mary Patetsos who stepped down as Chair of the Foundation at the conclusion of 2012. I thank her for the energy and passion she brought to the Committee.

Our supporters and donors are essential to helping us achieve our goals. On behalf of the Robinson Foundation Committee and members of the Robinson Institute, thank you for your ongoing support. As we build momentum and plan our strategy for 2013 and beyond, we hope that you will join us in our new direction and help us spread the word about the Institute's vital research, which needs ongoing support.

Neil Howells
Chair Robinson Foundation

The Robinson Foundation was established in February 2010 to support the life-giving research of the Robinson Institute, with the aims of:

- > Raising vital funds required to seed new areas of innovative research, to support the development of our next generation of scientists, and to fund special enabling equipment. This will form an integral part of building the capacity of the Institute
- > Raising public awareness of the clinical and policy benefits of the work of the Robinson Institute in order to enhance the uptake of research findings from the Institute by the community

To achieve this, the Robinson Institute works closely with the Robinson Foundation Committee, who generously offer their time, support and expertise. In 2012, Mr Neil Howells was appointed Co-Chair of the Committee, in preparation of the departure of Chair Ms Mary Patesos in December 2012. The Robinson Institute and Committee would like to extend its sincere thanks to all members of the Foundation Committee past and present for their support and commitment. Their contribution since the Foundation commenced is greatly appreciated. In 2012 we also welcomed Ms Joanna Close and Dr Dyann Smith to the Foundation Committee and look forward to working with them.

Engagement

In 2012 the Robinson Foundation continued to engage with the community to raise awareness of the Robinson Institute's research. Two key events were held - a corporate engagement dinner hosted by Adelaide BMW, and the Excellence in Research Seminar Series hosted by Macquarie Private Wealth in Adelaide.



Corporate Engagement Dinner at Adelaide BMW

This exclusive Foundation Dinner was held on 1 October and showcased the Institute's research into the causes, prevention and health implications of preterm birth. Preterm birth is a major global health issue with 15 million babies born preterm each year. It is the biggest killer of babies worldwide and is only second to pneumonia in children less than five years old. In Australia 8% of babies are born preterm, with neonatal intensive care costing around \$3,000 per day.

Professor Claire Roberts, a specialist in placental development and pregnancy complications, shared the many challenges that these babies face and the work that is being undertaken in the Robinson Institute to improve outcomes. Guests were treated to an intimate presentation and discussion to better understand preterm birth.

We thank Adelaide BMW for their generosity in hosting the event, and our guests for their attendance and ongoing support.

Excellence in Research - Macquarie Private Wealth

The Excellence in Research Seminar Series is presented by Macquarie Private Wealth, and provides insight into significant research within each of the University of Adelaide's five research institutes. The Robinson Institute participated in the 2012 series - with Emeritus Professor Alistair MacLennan sharing the latest research into the prevention of cerebral palsy.

Cerebral palsy is the most common physical disability in childhood. It affects over 34,000 Australians with a child being diagnosed every 15 hours. It is more common than every type of childhood cancer combined and there is no cure. The economic burden to Australia is more than \$4 billion annually and rising – yet relatively little progress has been made in its prevention and cure. The Robinson Institute has recently taken some remarkable steps toward prevention – making a major genetic breakthrough by undertaking the world's largest landmark study. The success of this was due to the 4,300 participants recruited and this could not have happened without the generous support of Macquarie Private Wealth and other donors.

Through the Excellence in Research Dinner hosted by Macquarie Private Wealth on 29 February, an incredible \$33,000 was raised for cerebral palsy research. The funds raised were directed toward the study and helped expand the Robinson Institute's recruitment efforts. The Institute now holds the world's largest collection of DNA from children with cerebral palsy and their mothers. We thank our generous supporters for their donations. We also thank Macquarie Private Wealth for not only hosting the event but also their generosity in matching the donations pledged and raised on this occasion.

The findings, which were uncovered as a result of this study, have had an enormous impact. They demonstrate that if a child or mother carry certain gene sequences they are more likely to develop cerebral palsy. Furthermore, the risk of particular subtypes of Cerebral Palsy increases when the mother had an infection during pregnancy.

The researchers also found that some events which occur during pregnancy increase the



Research funded in 2012 is as follows:

Lead researcher	Project overview	Funding
Associate Professor Michael Stark	Effect of Pre-Transfusion Washing of Red Blood Cells on Neonatal Outcome: a randomised control trial	\$20,000
Dr Julia Pitcher	Diurnal cortisol rhythms and the awakening response in preterm and term-born adolescents	\$20,000
Professor Michael Davies	Can we reduce the risk of preterm labour after infertility treatment?	\$10,000
Associate Professor David Parsons	Microscope camera for CF Research Laboratory	\$4,700
Emeritus Professor Alistair MacLennan	Examining the genomics of Cerebral Palsy	\$30,000

risk of cerebral palsy. These include pre-term birth and growth restriction, i.e. twins sharing the womb. It is however important to recognise that whilst the combination of genes and infection does trigger some types of cerebral palsy, the causes are varied and complex, and further research is required.

Where to next?

These new insights into cerebral palsy have significant implications. Using genetic markers, it may now be possible to identify children with an increased risk of developing cerebral palsy before they are born. Clinicians could then focus on reducing 'trigger events' that may occur during pregnancy.

While some genetic links have been found there is still much more to discover. The group examined just 39 of the DNA letters within each person's genome of more than 3 billion.

The Robinson Institute is committed to continuing this important research and will support the team in its fundraising efforts. In particular, funds are needed to repeat studies in Australia in a new and bigger cohort and to perform RNA sequencing studies (gene expression) and pathway analyses to help identify candidate genes causing cerebral palsy. Ultimately, the aim is to develop long term intervention strategies to prevent cerebral palsy.

Foundation funding program

In 2012 the Robinson Foundation raised a total of \$52,346 to support new or ongoing research. This, along with rolled over funds, was allocated through the Robinson Institute's funding program. Decisions around how funding is allocated is assessed through a rigorous process by an independent scientific research panel. This enables the Institute to invest in areas that are of critical importance, ranging from specific facilities and equipment to support for vital research trials.

Robinson Foundation Committee

Ms Robyn Brown
 Ms Joanna Close
 Mr Stephen Couche
 Mr Sathish Dasan
 Mr Neil Howells (Co-Chair)
 Mr Tim Hughes
 Emeritus Professor Colin Matthews
 Ms Julie Mitchell
 Mr Ian Nightingale
 Ms Mary Patetsos (Co-Chair)
 Dr Dyann Smith
 Ms Ruth Vagnarelli

Peter Couche Foundation



The Stem Cell for Stroke Group continues to be the only group in the country attempting to solve the stroke puzzle through the application of non-embryonic stem cells.

As the population continues to age and our increasingly sedentary lifestyles suffer from both increased stress and decreased dietary quality, the importance and relevance of the research output from the Group continues to grow.

Stroke is a huge and rapidly growing problem within the community. It is through the support of this Group, through the Foundation, that we not only seek to keep abreast of developments abroad but to significantly influence such developments.

To this end thank you for the support from our donors, we have raised \$153,723 this past year, bringing the total raised to more than \$460,000.

Peter Couche

Overview

Peter Couche was a successful stockbroker and father of three when he suffered a stroke at age 42 (over 20 years ago). Peter's stroke left him a quadriplegic with "locked-in syndrome". He cannot speak and has little muscle control but has an active and alert brain, and is determined to make a difference to those who have suffered a stroke.

In association with the University of Adelaide, Peter established the Peter Couche Foundation in 2009 to increase awareness of stroke and raise vital funds to support the Robinson Institute's Stroke Research Program.

Led by renowned stroke physician and researcher Professor Simon Koblar, the team is currently researching the use of stem cells from the adult human tooth, called dental pulp stem cells (DPSCs), as a potential therapy for brain repair in stroke victims.

Research to date has indicated that DPSCs have an ability to produce neurons (brain cells) and make a range of growth factors which are likely to help repair the brain.

Since launching in 2009, the Foundation has raised more than \$460,000 (to the end of 2012), with \$153,723 being raised in 2012 alone to progress this important research.

Major research developments and fundraising initiatives are outlined below; with other key activities including the Foundation's involvement in the People's Choice Credit Union Lottery and the fundraising efforts of Tim Kaethner through his participation in the Barossa Marathon.

From all of our researchers and the team at the Peter Couche Foundation we would like to thank our generous donors and supporters. Through your ongoing collaboration we have significantly progressed this important research agenda which could aid stroke sufferers in the near future.

Research Developments

Australian research regarding stem cell therapy in stroke is at an exciting crossroad. The Peter Couche Foundation has achieved a great deal in raising the profile of this type of therapy for stroke - funding the first research project to show how human adult stem cell treatment from the tooth improves brain function.

In 2012 the Stem Cells Transitional Medicine Journal published the three year outcomes of Simon's study of how DPSCs can be used to reduce damage to the brain following a stroke. The paper provided strong evidence to encourage the ongoing use of DPSCs for brain repair for future clinical use.

In 2012 research focused on comparing results obtained from the direct injection of DPSCs into the brain 24 hours following a stroke with new work investigating intravenous injections. This significant body of research found that intravenous injections of stem cells into a patient's arm following a stroke is a safer method to adopt as opposed to administering the cells directly to the brain. The Group also investigated if later intravenous injection of stem cells (2 weeks after a stroke) will be effective.

The Group was pleased to announce in 2012 that Australian biotechnology company, Mesoblast, agreed to partner with the University of Adelaide. Mesoblast intends to use the group's findings to conduct further research in pre-clinical studies and work towards a clinical trial in the future. Mesoblast will draw heavily from the group's findings, both current and ongoing. The majority of funds raised through the Peter Couche Foundation in the future will continue critical DPSC research.

Professor Simon Koblar also continued his collaboration with the University of Cambridge and the world renowned Cambridge Centre for Brain Repair to further understand how stem cells may repair the brain. Answering this fundamental question is crucial, as it allows researchers to improve ways to use stem cells in the future.

In 2012, the Foundation funded the inaugural Peter Couche Fellowship, which was awarded to Dr Karlea Kremer. Additionally, Simon was made a full Professor of the School of Medicine, an honour truly deserved.

2012 Activities

Inaugural Peter Couche Fellowship Awarded

Dr Karlea Kremer, a Postdoctoral Fellow in the Stroke Research Program, was awarded the first Peter Couche Foundation Fellowship in 2012.

Karlea holds a Bachelor of Medical and Pharmaceutical Biotechnology and completed her Honours and PhD with the Adelaide Cystic Fibrosis Gene Therapy Research Group, which sparked her interest in stem cell research. Her current research looks at human dental pulp stem cells and how they can be used in the repair of brain damage caused by stroke.

Karlea says the fellowship will allow her to complete her research investigating the characteristics of DPSC delivery for optimum functional improvement.

"Currently help is only given to make life easier, while dealing with the damage caused, not repairing the damage itself", Karlea said.

"The highlight of my career so far, has been having the opportunity to be involved in research that is innovative and one of the most advanced projects for using stem cell therapy in stroke in Australia. It is also a project that is showing real promise for translation to the clinic in years to come."

The Peter Couche Foundation is proud to support young scientists like Karlea to keep these brilliant minds in Adelaide and Australia to pursue innovative stroke research.



Peter Couche Foundation Annual Wine Dinner

In November, over 170 supporters attended the Peter Couche Foundation annual Wine Dinner and through their generosity raised \$42,000 for stroke research.

Held at the National Wine Centre in Adelaide, guests were treated to a three course meal matched with premium wines, heard from leaders in the wine industry and enjoyed entertainment from local singer Michelle Nightingale and Acoustic Juice.

On the evening MC Kate Collins interviewed research leader Professor Simon Koblar who gave an insight into 'locked in syndrome' and how this affects Peter's life.

The event was also an opportunity for Peter to meet the many supporters of the Foundation.

Thank you to all our sponsors and auction contributors, your valued support made the event a success. In particular we would like to recognise the generosity of Orlando Wines, Holco, Raw Pearls and the National Wine Centre.

Don't Speak: Silence for Stroke

What would your life be like if you couldn't speak? Couldn't express an opinion, ask a question or tell your children that you love them?

This is the question we ask our supporters who participate in the 'Don't Speak Silence for Stroke' annual fundraising campaign. Peter Couche and thousands of stroke sufferers like him across Australia know exactly how this feels.

Approximately 60,000 people suffer a stroke in Australia every year which can result in loss of memory, speech or movement. Don't Speak aims to raise awareness of the impact that stroke can have on an individual, their colleagues, families and friends by asking participants to be silent for at least one hour.

In 2012, 39 Don't Speak participants pledged to be silent for at least an hour and sought sponsorship to support the cause. They successfully raised more than \$41,000. Congratulations to Andrew Brown from Adrian Brien Automotive for being the top fundraiser!

Thank you to our ambassador Tom Harley for his continued support of Don't Speak and raising awareness of the Peter Couche Foundation.

Adtrans Golf Day celebrates 25 years

In November Adtrans Automotive Group celebrated 25 years of supporting the community through its annual Charity Golf Day, having raised over \$1.2 million to support local charities during this time.

In 2012 the day was once again an incredible success with \$20,000 being donated to the Peter Couche Foundation.

Thank you Adtrans for your enthusiasm, hard work and continued support of the Peter Couche Foundation.

Santos 3 year sponsorship

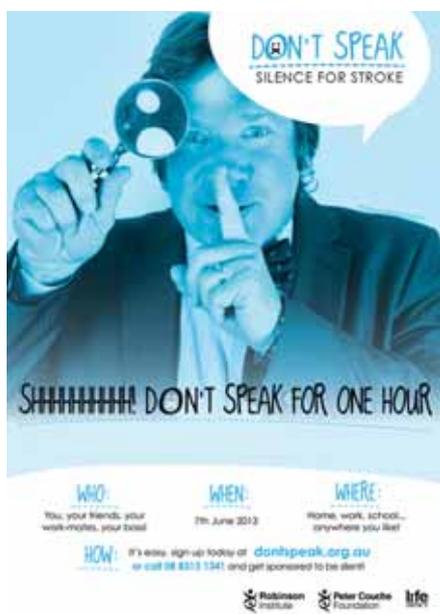
Since the inception of the Peter Couche Foundation in 2009 Santos has been a founding partner.

In 2012, Santos donated \$20,000 as part of a 3 year sponsorship valued at over \$60,000 to support stroke research.

Santos provides great support to the community and we value their commitment to the Peter Couche Foundation.

Peter Couche Foundation Committee

- Mr Dom Cosentino
- Mr Peter Couche
- Mrs Simona Couche
- Mr Colin Dunsford
- Mr Andrew Ford
- Ms Alissa Nightingale
- Mr Stephen Officer
- Mr Mick Scammell
- Ms Lisa Taplin



Research capacity building

To achieve a vision of becoming a world leader in life-supporting scientific and clinical research by 2020, the Robinson Institute is investing in people, networks and facilities.

To build skills, confidence and leadership in our current and future researchers, the Institute delivers a number of programs and scholarships.

Mentoring program

The Mentoring Program was established as an important step to career orientation and personal development for members of the Robinson Institute. Mentors – typically senior researchers or research leaders – volunteer their time to mentor early-career researchers and offer to support them in career and skills development. Mentees are matched with Mentors according to their research interests and specific requirements. The program has now run for three years and has proven to be of great benefit to both Mentees and Mentors.

The purpose of the Robinson Institute Mentoring Program is to:

- > Develop and support researchers in their respective career stages
- > Increase the skills of members
- > Develop an awareness of the importance that networking can have on future career opportunities, and commence appropriate networking activities
- > Facilitate relationship-building amongst members of the Institute, as a potential for future collaboration
- > Provide empowerment opportunities where members can engage in leadership roles
- > Enhance researcher credentials for CVs, grants and other applications
- > Help members to gain an understanding of the broader Institute activities and initiatives, how they fit into the Institute and the value and potential of the work they do from a broader perspective

In 2012 the mentoring program brought together 18 Mentors and Mentees, creating nine successful partnerships.

One of these partnerships was between senior researcher Associate Professor Jeremy Thompson, and early career researcher Dr Sebastian Doeltgen. Both participants had a positive experience, particularly Sebastian who felt it provided him with a competitive edge.

“It really helped me to look at my career path in the bigger picture and offered the opportunity to assess various options more objectively. It really can increase one’s competitiveness and it gives you a certain edge and focus on what is really relevant,” said Sebastian.

Professional development

The Robinson Institute is committed to investing in ongoing professional development for its researchers. In 2012, the Institute ran ‘Pitch Training’ to improve presentation skills, confidence and science communication. Participants were involved in a group workshop and benefitted from one on one coaching sessions.

Equipment grants

To ensure members receive adequate coverage of the equipment costs associated with research, the Robinson Institute provides seed funding to members who receive NHMRC Equipment Grant funding. In 2012 the following equipment grants were awarded:

Equipment grants		
Equipment	Amount	Lead researcher
Rapid Rate Transcranial Magnetic Brain Stimulator, stimulating coils and electrophysiological recording	\$16,440	Dr Julia Pitcher
BIORAD CFX96 Touch Real-Time PCR Detection System	\$12,812	Professor Sarah Robertson
Nikon Eclipse Ti-U Inverted Research Microscope, monochrome digital camera (for fluorescence), colour digital camera (for stained cells) and NIS-Elements AR Imaging Software	\$9,941	Professor Claire Roberts
Agilent Bio-Analyser	\$7,200	Associate Professor Simon Barry
TECAN HydroFlex Microplate Washer, with liquid level detection, magnetic bead separation plate and low level vacuum filtration plate	\$5,017	Associate Professor David Kennaway

Jeffrey Robinson Honours Scholarship

In 2012, the Robinson Institute offered the Jeffrey Robinson Honours scholarship to an outstanding Honours student, Katherine Watson.

During her undergraduate study at the University of Adelaide, Katherine developed a keen interest in menstrual disorders and reproductive immunology. Her honours project 'The influence of seminal plasma on pathogenic processes in endometriosis' reflected these interests, and was a joint project with the Endometriosis Group and the Reproductive Immunology Group. Katherine's supervisors were Dr Louise Hull (primary supervisor), Professor Sarah Robertson and Dr Jonathan McGuane.

For Katherine, receiving the Jeffrey Robinson scholarship was highly rewarding. It allowed her to reduce the need for part time work, freeing up more time for study and other interests.

"This generous scholarship allowed me to undertake extra-curricular activities such as my involvement with Insight (The University of Adelaide's global health group) and the Australian Medical Student Association global health committee," said Katherine.

In her Honours year Katherine developed her writing skills through creating research proposals, literature reviews and her thesis. She also conducted a range of laboratory work including endometrial cell culture, treating cells with seminal plasma and measuring supernatants using ELISA and Luminex assays. Katherine was also able to use mouse models to test treatments.

"Using human endometrial tissue in a xenograft model – which required operating on the mice – I transplanted the tissue and administered intraperitoneal treatments. Each replicate experiment took around six weeks to complete," said Katherine.

But the real highlight for Katherine was the range of people she was able to work with and their willingness to help her succeed beyond her Honours year.

"Without a doubt, the highlight was the people I got to work with. I think the biggest opportunity that has been given to me so far is the interactions I have had with different researchers", said Katherine.

"People have gone out of their way to help me meet people they thought could provide me with some guidance and direction beyond my honours year, and these conversations have been extremely valuable."

Katherine is currently in the process of completing her Honours research work with a view to submitting it for publication. The research has already been presented at several conferences, including the RANZCOG regional scientific meeting in Darwin, May 2013.



Cook Medical Fellowship

Cook Medical is a world leader in the commercial production of new IVF technologies and products, including culture media, devices and equipment. The aim of the Cook Medical Adelaide Fellowship program is to facilitate new, ongoing and long-term collaborations between Adelaide and China. This includes supporting prominent young researchers in both Australia and China, and strengthening the depth and quality of the research programs within the Robinson Institute and respective universities and institutions in China.

In 2012 two Cook fellowships were awarded to researchers from the People's Republic of China to support research activities at the Robinson Institute:

- > Dr. Jing Du, Associate Researcher in the Department of Reproductive Genetics in the World Health Organisation Collaborating Centre for Research in Human Reproduction in Shanghai
- > Associate Professor Xiaoying Zheng, Clinical Embryologist at Peking University Third Hospital in Haidian District, Beijing



Associate Professor Xiaoying Zheng's experience:

Xiaoying is a Clinical Embryologist who applied for the Cook Fellowship in order to gain further research experience to improve her clinical practice as well as her research.

Xiaoying is working with Dr Robert Gilchrist and Associate Professor Jeremy Thompson on oocyte biology, in particular in vitro maturation of oocyte. Her aim is to find the best method to improve oocyte development potential. Xiaoying believes that having the chance to work with Rob and Jeremy has developed her understanding of research program design and has exposed her to valuable new methods.

Xiaoying has found Adelaide to be a beautiful city and hopes to continue her collaborations with the Robinson Institute when she returns home to Peking University Third Hospital.



Dr. Jing Du's experience:

With many research interests in common, Jing is now working with Professor Claire Roberts' Placental Development Group looking at the impact of genetics on infertility. Jing's research addresses the identification of genes involved in complex human diseases, as well as the identification of the evolutionary and demographic forces that influence the origin, maintenance, and distribution of genetic disease in humans. Over the duration of his time in Adelaide, Jing's specific tasks will be to:

- > Write a systematic review about genetic and epigenetic variants in small for gestational age pregnancies
- > Work with the Adelaide arm of the SCOPE project
- > Assess the differential expression of microRNAs that target the IGF2 gene between normal and adverse pregnancy outcomes.

Jing enjoys her research and working life at the Robinson Institute, and is very grateful for the opportunity to work in South Australia. "Adelaide is a quiet and green city. I like its food, culture, its long beaches, beautiful hills and especially the hospitality of Aussies," said Jing.

Through receiving the scholarship, Jing hopes to further develop her own and the Institute's research ability, and strengthen collaborations outside of China.

Training the next generation

The Robinson Institute is committed to training the next generation of researchers through Honours and Higher Degree by Research programs. In 2012 the Institute had more than 30 Honours students and 110 PhD students. As an integral aspect of both programs, students receive supervision from world-leading experts in their chosen fields, and have access to training and development programs. The Institute also awards an Honours scholarship each year to support an exceptional student in honour of Emeritus Professor Jeffrey Robinson.

Travel grants

The Travel Grant Program is a joint initiative between the Robinson Institute and the School of Paediatrics and Reproductive Health. It provides Robinson Institute members with the opportunity to present and share their research findings at national and international conferences and meetings. By attending such events, researchers are able to network with interstate and overseas researchers, expand their CVs and develop relationships for future collaborations. In 2012, 42 researchers were awarded travel grants.

Lisa Akison	Endocrine Society of Australia and Society for Reproductive Biology Annual Scientific Meeting	Gold Coast, Australia
Emily Bain	Perinatal Society of Australia and New Zealand Annual Congress 2013	Adelaide, Australia
Anna Brown	54th American Society of Haematology Annual Meeting and exposition and myeloid stem cell development workshop	Atlanta, Georgia, USA
Sam Buckberry	Society for Reproductive Biology and Australian and New Zealand Placental Research Association	Gold Coast, Australia
Peck Yin Chin	Society for Reproductive Biology and Australian and New Zealand Placental Research Association	Gold Coast, Australia
Wing Hong (Vincent) Chu	Endocrine Society of Australia and Society for Reproductive Biology Annual Scientific Meeting	Gold Coast, Australia
Pallave Dasari	Mammary gland biology research seminar and mammary gland biology Gordon Research Conference	Barga, Italy
Martin Donnelley	Medical Applications of Synchrotron Radiation	Shanghai, China
Tod Fullston	Society for the Study of Reproduction 45th Annual Meeting	Pennsylvania, USA
Tod Fullston	Australian Health and Medical Research Congress 2012	Adelaide, Australia
Mani Ghanipoor Samami	33rd Conference International Society of Animal Genetics	Cairns, Australia
Mitchell Goldsworthy	42nd Annual Meeting of the Society for Neuroscience	New Orleans, USA
Nardhy Gomez-Lopez	59th Annual Meeting of Society for Gynecologic Investigation 'Improving Women's Health through Personalised Medicine'	San Diego, USA
Emer Heatley	The Federation of Asia and Oceania Perinatal Societies and Perinatal Society of Australia and New Zealand Annual Congress 2013	Sydney, Australia
Amanda Hight	Society for Reproductive Biology and Australian and New Zealand Placental Research Association	Gold Coast, Australia
Nicolette Hodyl	5th Society for Gynecologic Investigation International Summit Meeting 'Prematurity and Stillbirth: antecedents, mechanisms and sequelae'	Brisbane, Australia
Ali Javadmanesh	33rd Conference International Society for Animal Genetics	Cairns, Australia
Zohra Kamran	Perinatal Society of Australia and New Zealand Annual Congress 2013	Adelaide, Australia
Jessica Laurence	Endocrine Society of Australia and Society for Reproductive Biology	Gold Coast, Australia
Hong Liu	26th fetal and neonatal workshop of Australia and New Zealand	Port Stephens, Australia
Noor Lokman	Frontiers in Cancer Science 2012 and CSH Asia/ International Cancer Microenvironment Society Joint Conference on Tumour Microenvironment	Singapore and China
Jonathan McGuane	Endocrine Society of Australia and Society for Reproductive Biology Annual Scientific Meeting	Gold Coast, Australia
Jonathan McGuane	Society for Gynecologic Investigation Annual Scientific Meeting	Orlando, Florida
Gai McMichael	4th International Cerebral Palsy Conference	Pisa, Italy
Ezani Mohamed Jamil	Endocrine Society of Australia and Society for Reproductive Biology Annual Scientific Meeting	Gold Coast, Australia
Siti Noor Din	42nd Annual Scientific Meeting of the Australasian Society of Immunology	Melbourne, Australia
Michael O'Callaghan	4th International Cerebral Palsy Conference	Pisa, Italy
Nicole Palmer	Society for the Study of Reproduction 45th Annual Meeting	Pennsylvania, USA
Nicole Palmer	International Congress of Andrology	Melbourne, Australia
Julia Pitcher	2nd International Workshop on Synaptic Plasticity	Taormina, Sicily, Italy
Dulama Richani	Society for the Study of Reproduction 45th Annual meeting	Pennsylvania, USA
Rebecca Robker	ENDO 2013 - annual meeting of the USA Endocrine Society	San Francisco, USA
John Schjenken	Endocrine Society of Australia and Society for Reproductive Biology Annual Scientific Meeting	Gold Coast, Australia
Luke Schneider	42nd Annual Meeting of the Society for Neuroscience	New Orleans, USA
Michael Stark	5th Society for Gynecologic Investigation I International Summit Meeting 'Prematurity and Stillbirth: antecedents, mechanisms and sequelae'	Brisbane, Australia
Jaqueline Sudman	Ovarian Club	Prague, Czech Republic
Zhixian Sui	Obesity 2012 - 30th annual scientific meeting of the AOS	San Antonio, USA
Deborah Toledo	6th International Symposium in Vertebrate Sex Determination	Kona, Hawaii
Ann-Maree Vallenge	Neuroscience 2012	New Orleans, USA
Megan Warin	12th European Association of Social Anthropologists Conference	Paris, France
Linda Wu	Annual Endocrine Society of Australia Seminar	Torquay, Australia
Ruidong Xiang	33rd Conference International Society for Animal Genetics	Cairns, Australia

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This acknowledges the 2012 membership of the Robinson Institute; we have aimed to capture as comprehensive a list as possible and any omissions are unintentional. We would like to recognise the contribution of all members, with a special mention to the School of Paediatrics and Reproductive Health's administration team led by Michael Guerin, School Manager.

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Mohanasundaram, Daisy	Ricciardelli, Carmela	Szeyan, Cheung	Wright, Megan	
	Richani, Dulama	Tan, Izza	Wu, Linda	
			Xafis, Vicki	

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For further enquiries

The Robinson Institute
Ground Floor, Norwich Centre
55 King William Rd, North Adelaide
University of Adelaide, SA 5005

Telephone: +61 8 8313 8166

Freecall: +61 8 8313 1355

Email: robinsoninstitute@adelaide.edu.au



robinsoninstitute.edu.au



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