



Telethon Institute for  
Child Health  
Research

OUR DIRECTOR PROFESSOR JONATHAN  
CARAPETIS WITH BABY REMY

The Telethon Institute for Child Health Research is affiliated with The University of Western Australia through the Centre for Child Health Research and has strong clinical research links to Princess Margaret Hospital for Children.



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# working together

*COMING TOGETHER IS A BEGINNING, STAYING TOGETHER IS PROGRESS, AND WORKING TOGETHER IS SUCCESS.*

- HENRY FORD

Long gone are the days where research was conducted in isolation – where an individual scientist would make a startling discovery staring down a microscope or at statistics.

Today's scientific endeavours are bigger in scope and scale, driven by huge amounts of data that have been unleashed by the mapping of the human genome and our ability to delve deeper into the biological, social and environmental factors that affect health and wellbeing.

It's complex work to tackle complex problems, and requires a multi-pronged approach.

That's why today's best research organisations are working together, harnessing the power of their collective activities.

But that's not enough.

What about the clinicians, the families, the policy makers and the communities who might have different questions and insights?

The new strategic plan of the Telethon Institute for Child Health Research recognises the importance of all these partnerships.

Working together we see a much more detailed picture than we can working apart.

The result?

Research that is more relevant and responsive to community and clinical needs.

Research that results in knowledge being shared and valued.

This report features just some of our collaborations.



**FOR MORE INFORMATION GO TO [CHILDHEALTHRESEARCH](http://CHILDHEALTHRESEARCH).**

# ABORIGINAL HEALTH

## The Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW)

### Overview

The Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW) is a strategic program of intervention research that is focused on achieving radical and sustainable change for the Aboriginal community and improving the lives of Aboriginal people. The program is a unique validation of Aboriginal knowledge and demonstration of Aboriginal methodology involving a multi-disciplinary team of Aboriginal and non-Aboriginal researchers, who will contribute to the body of knowledge, work transparently with the Aboriginal community and embrace Aboriginal culture and ways of thinking.

The CREAHW brings the research strengths of each of the Chief Investigators together in a cohesive program of community-based intervention research, well known both nationally and internationally, but with local relevance to Western Australia. It will be supported by the outstanding track record of the Telethon Institute for Child Health Research in working with government and informing policy and practice and build on past achievements by developing the next generation of Aboriginal health researchers and leadership among the Chief Investigator team.

The CREAHW team program of research will build capacity in the community and bridge the disconnection between researchers, service

providers and the community in a practical and empowering way. History has seen significant issues, such as racism, perpetuated and become embedded in the Aboriginal community with a significant negative impact on health and wellbeing. The CREAHW investigators are seeking to change this cycle by listening and working in partnership with the community and investing energy and attention to get the best result for the community. This will require system change and involve investing time with decision makers in order to inform policy and practice.

*Funders of the project: In 2010, the National Health and Medical Research Council awarded the Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW) grant to a group of 10 Chief Investigators (CI) headed by Professor Fiona Stanley AC (Director, Telethon Institute for Child Health Research). The CREAHW is a collaborative research venture between seven research institutions, and is funded with a grant of \$2.5m over five years.*

The CREAHW has several Chief Investigators and their individual and collaborative research projects aim to answer specific research and policy relevant questions within Aboriginal Health and Wellbeing. Projects being undertaken by researchers at the Telethon Institute are as follows:

### LOOKING FORWARD: IMPROVING MENTAL HEALTH SERVICE OUTCOMES FOR ABORIGINAL PEOPLE LIVING IN THE SOUTH-EAST METROPOLITAN CORRIDOR

MICHAEL WRIGHT, FIONA STANLEY

This project is a partnership between Aboriginal families<sup>[1]</sup>, government and non-government mental health service providers, primary health-care providers (GP's) Aboriginal Medical Service, and the Telethon Institute for Child Health Research.

The goal of this project is to increase the effectiveness of the public mental health services for Aboriginal families whose lives are affected by serious mental illness living in the south-east metropolitan corridor. The project will engage service users, Aboriginal and non-Aboriginal service providers, policy makers and managers.

The project aims to develop in consultation with service users (Aboriginal families) and service providers a culturally safe mental health framework that will assist in the delivery of mental health services to Aboriginal families living in the south-east metropolitan region.

The methodology for the project includes conducting a series of community forums across the region. The forums commenced in March 2011 and will extend for a period of 18 months, finishing in July 2012. A report will be published and released at the end of 2012. The project is expected to be completed at the end of 2013.

*Funders of the project: NHMRC are funding the lead researcher.*

### IMPLEMENTING THE AEDI IN THE WESTERN DESERT

ROZ WALKER

The key objective of this research project is to improve the maternal and child health and wellbeing of Martu communities living in the Western Desert communities of Jigalong, Punmu, Parngurr and Kunawarrtji and Newman in the Pilbara. The project is undertaken in partnership with funding through BHP Billiton Iron Ore, Indigenous Community Investment Program 2010-2014. Using Community-based Participatory Action Research methods the project provides the evidence base and conceptual underpinnings to inform and evaluate the new maternal and child health initiatives being developed by World Vision Australia and other stakeholders to improve the social, educational and maternal and child health and wellbeing outcomes of the Western Desert communities.

Specifically the project involves implementing, communicating and disseminating the AEDI results to relevant stakeholders in health and education Aboriginal across the Western Desert communities over the five years 2010-2014. It also involves trialling appropriate tools and communication strategies to share the information with Aboriginal families to build of their knowledge and strengthen community capacity. There is strong research evidence which confirms the benefits of using the Early Development Index to bring about community level change in Australia and in Canada.

<sup>[1]</sup> The word 'Aboriginal' has been used in this application to refer both to the Aboriginal and Torres Strait Islander people of Australia as well as other Indigenous groups residing in other parts of the world. The author acknowledges that Aboriginal and Torres Strait Islander people may identify with their local clans or group name and he means no disrespect in using the term Aboriginal.

## CONNECTION, BELONGING AND HEALTH OF AUSTRALIAN ABORIGINAL PEOPLE AND THEIR COMMUNITIES IN THE CITY OF SWAN AND THE PILBARA REGION OF WESTERN AUSTRALIA.

RHONDA MARRIOTT, FIONA STANLEY, NICK DE KLERK, CHERYL KICKETT-TUCKER, ROZ WALKER & DENISE GROVES

This holistic, 4 year qualitative study will explore the relationship between connection and belonging for Aboriginal people living in the City of Swan and the Pilbara with health outcomes to develop a conceptual framework. This important and original work will add to the paucity of knowledge in this area. The researcher will apply a community participatory action research approach and thus, engage with the community at all steps in the research project. A conceptual framework will evolve from the research data and this will be applied to selected health priorities: for example, the relationship of Aboriginal spirituality and birthing on country. The work will also test the phenomenological variant of ecological systems theory (PVEST) (Spencer, Dupree and Hartman, 1997; Spencer, Fegley and Dupree, 2006) in understanding cultural resilience and its relationship with connection, belonging and health. This important and original work will add to the paucity of knowledge on resilience and health outcomes. Recommendations will drive health policy; build community resilience and capacity; inform non-Aboriginal health care professionals' understanding of the need for culturally appropriate health care services; guide health professionals' practice; and guide health policy for the provision of culturally appropriate health services.

## STRENGTHENING SOCIAL AND EMOTIONAL WELLBEING OF AUSTRALIAN ABORIGINAL PEOPLE: HOW DOES RACIAL IDENTITY AND RELATED SELF-ESTEEM MEDIATE THE MENTAL WELLBEING OF ABORIGINAL PEOPLE?

CHERYL KICKETT-TUCKER

This is an extension of Cheryl Kickett-Tucker's research on the development of racial identity and related self-esteem of Aboriginal children, youth and adults (using her IRISE measures across the life span). This research will describe the mediating factors of racial identity and related self-esteem in relation to Aboriginal people's mental wellbeing and identify effective ways to strengthen the social, cultural and emotional wellbeing and identity of Aboriginal children, youth and young adults onwards. This research will encompass development of new instrumentation, complemented by in depth personal interviews using Community Participatory Action Research (CPAR) methods.

## CONSULTING WITH THE COMMUNITY TO DEVELOP AN INNOVATIVE AND CULTURALLY RESPONSIVE EMPOWERMENT, HEALING AND LEADERSHIP PROGRAM

PAT DUDGEON, ROZ WALKER, CLAIR SCRINE, CHERYL DUNKLEY, DIVINNA D'ANNA, & KATHLEEN COX

The project is being done in collaboration with Kimberley Aboriginal Medical Services Council (KAMSC) Social Emotional Wellbeing Unit. This project stems from the high rates of Suicide in the Kimberley in 2010. The aims of this project

are to strengthen the capacity of community members to empower themselves and others to change their lives, their communities and the systems that are barriers to good social and emotional wellbeing. The findings will be used to develop an accredited innovative program that is culturally appropriate to the empowerment of Aboriginal people in different geographical locations. The project consisted of the following two stages - community and stakeholder consultation; program development.

A Final Research Report, Hear Our Voices, was launched in March 2012 and following its launch Community Empowerment, Healing and Leadership workshops have been developed and piloted in the Kimberley. Consultations are currently underway for the further development and implementation of these workshops throughout Australia.

## CULTURAL SECURITY FOR YAMAJI (ABORIGINAL PEOPLE) WITHIN HEALTH SERVICES IN THE MIDWEST MURCHISON REGION OF WESTERN AUSTRALIA.

JULI COFFIN

This project aims to create a culturally secure health service for Yamaji (Aboriginal people) in the Midwest/Murchison region of Western Australia. This will be achieved through the mapping of current policies and practices when treating and engaging Aboriginal health consumers across all health sectors, implementation of the 'Cultural Security Framework' (Coffin 2007) within each health sector to show the strengths and weaknesses for priority, and working within each health sector

to create strategies/policies and practice to improve areas of weakness.

It is hoped that this project will provide evidence that changes can be culturally secure and sustainable. This project will also take into consideration the existing Department of Health Cultural Respect Implementation Framework and other documentation/policies in regard to this issue. An arm of the Cultural Security project in the North Metropolitan region has also been established through the PindiPindi Centre as part of improving culturally secure health service delivery to Aboriginal people in the North Metropolitan Health Service Area. This will ensure great research translation across rural, remote and urban settings of the proposed methodology and model. The Framework strategies and actions will be developed by the Cultural Security Aboriginal Leadership Group; this group will provide practical implementation guidance and cultural advice to the program.

## WESTERN AUSTRALIAN ABORIGINAL INTERGENERATIONAL FETAL GROWTH STUDY (WAAIFS)

SANDRA EADES, BRIDGETTE MCNAMARA, GLENN PEARSON, AMANDA LANGRIDGE, CARRINGTON SHEPHERD, NICHOLAS DE KLERK & FIONA STANLEY

This project will investigate determinants of fetal growth across generations, in all Aboriginal mothers and children born in Western Australia between 1980 and 2009, using a novel measure of fetal growth; the percentage of optimal birth weight (POBW). POBW measures the appropriateness of fetal growth for a given gestational age, fetal gender, maternal height

and parity, and allows the prevalence and severity of both growth restriction and excessive growth to be assessed.

Using unique data from linked administrative health datasets spanning over 30 years and multilevel models, the study will map the differing contributions of fetal growth to chronic diseases in individuals, the links between maternal fetal growth and that of her offspring, and how the occurrence of medical conditions and pregnancy complications influences that relationship. We will explore the causal pathways involved in the perpetuation of sub-optimal fetal growth across generations, as well as those that are protective.

These investigations will be to inform whether the most important pathways to chronic disease began in grand-maternal environments or in the next generation. The results are likely to provide evidence for when maternal and child health interventions are likely to be most effective for the prevention of lifelong adult diseases including those influencing reproductive risks.

## FAMILY ASSESSMENT TOOL, MILLIYA RUMURRA, BROOME

DAWN BESSARAB

Milliya Rumurra (MR) is a residential centre providing treatment and rehabilitation to Indigenous community members wishing to address their misuse of alcohol and other drugs (AOD). Currently as part of their formal program MR assess all individuals attending the centre to develop a specific treatment plan to assist each person in addressing their AOD use while they are at the centre. The centre's

outreach program informally works with the family of the attending person to help them to understand what the centre is offering and to provide support while their member is receiving treatment. The outreach program also assists both the family and the client with their transition back into the family and community on completion of the program.

When looking at the health and social and mental well-being of their clients MR now want to integrate the support service that they offer to the families of their clients and develop a family assessment tool that can more effectively help their workers in developing a specific case plan that engages with the family during the rehabilitation process of their member. The current project is to work with the management, clinical and outreach team, clients, families, community members and service stakeholders to develop a family assessment tool. This tool will become an integral part of the MR's service and will be used by clinical and outreach team workers to assess the needs of the client's family at the time of intake. The project will utilize the community based participatory research approach. The aim of the assessment tool is to improve the health and quality of the Aboriginal client and their family during their journey through AOD treatment. The final outcome of the project will be the development of a family assessment tool which will be trialled by MR's clinical and outreach team and evaluated for its usefulness and effectiveness.

## Kulunga Research Network

### Overview

The aims of the Kulunga Research Network are to;

1. facilitate high quality research that is community based and culturally safe,
2. to develop the capacity of Aboriginal and non-Aboriginal people to conduct high quality research with Aboriginal communities,
3. to facilitate the translation of research into policy and practice and,
4. to act as an advocate for Aboriginal families in public policy development.

In addition to progressing its research projects, the focus of the team in 2011 has been on building relationships with communities and community-based organisations, and assisting government and non-government organisations to work effectively with Aboriginal people and ensure their messages are appropriate and effective. In addition, staff have been working collaboratively across TICHR with a number of projects.

### Strategic Planning

This year saw Kulunga deeply involved in the Institute's strategic planning process with a parallel but specific process initiated to capture feedback from a cross section of stakeholders. This process was led by Glenn Pearson (Manager Aboriginal Health Research) and with ongoing

support from Emerita Professor Rhonda Marriott and Dr Michael Wright feedback was drawn from the Chief Investigators of the Institute's Centre of Research Excellence for Aboriginal Health and Wellbeing (CREAHW) and the members of the Institute's the Aboriginal Collaborative Council Advising on Research and Evaluation (ACCARE).

Kambarang Consultancy Service was engaged to undertake a specific program of work to complement the feedback from the CREAHW and ACCARE processes and involved drawing together a literature review and completion of 15 one to one interviews comprised of a representatives from the Aboriginal community, state and commonwealth government and Aboriginal and non Aboriginal researchers. Kambarang also lead a community focus group process comprised of Aboriginal community members as well as community based organisations.

A final report with recommendations will be presented to the TICHR Director for consideration at the Strategic Management Committee.

## WORKING TOGETHER: ABORIGINAL AND TORRES STRAIT ISLANDER MENTAL HEALTH AND WELLBEING PRINCIPLES AND PRACTICE

ROZ WALKER (PROJECT LEADER), GLENN PEARSON (MANAGER, KULUNGA), JACQUELINE ANN BRADLEY (COMMUNICATIONS PROJECT OFFICER), PAT DUDGEON, (EXPERT CONSULTANT), AND CLINTON SHULTZ, (INDIGENOUS CONSULTANT).

*Working Together* was produced as an important resource to improve the capacity of Aboriginal

and non-Aboriginal health workers, mental health workers and relevant practitioners to identify and address mental illness and associated issues of substance misuse and suicide in Aboriginal and Torres Strait Islander communities, to recognise the early signs of mental illness and make referrals for treatment where appropriate. It is also intended for staff working in Healing Centres and Link-up agencies to address issues of grief, loss and trans-generational trauma associated with the impact of forced removal from families and /or country. The book is also intended for students working in courses in nursing, medical schools, social work, psychiatry, psychology and primary health care.

Since commencing distribution of *Working Together* in August 2010 over 35,000 hard copies of the book have been widely distributed to a broad range of target audiences. The on-going feedback and evaluation from both the survey monkey feedback, and student, practitioner and stakeholder evaluations confirms that the book is an important and effective resource for a range of health, allied health practitioners and educators and other professionals and agencies supporting and working with Aboriginal and Torres Strait peoples in mental health and wellbeing.

The Commonwealth Department of Health and Ageing have commissioned Kulunga and led by Associate Professor Roz Walker to complete a revised edition of this highly successful book which will be released in 2013.

Funders of the project: Office of Aboriginal and Torres Strait Islander Health

## The Aboriginal Collaborative Council Advising on Research and Evaluation (ACCARE)

### Overview

The Aboriginal Collaborative Council Advising on Research and Evaluation (ACCARE) was formed in 2008 to provide support and direction to Aboriginal research conducted through the Telethon Institute for Child Health Research (the Telethon Institute). ACCARE is a committee of the Institute Board advising on Aboriginal research.

The Council comprises a group of professional, passionate people committed to ensuring Aboriginal people and the wider Aboriginal community benefit from the research conducted through the Telethon Institute.

The goal and over-arching principles for the work of the Council is to ensure the facilitation, translation and application of research findings into policy and practice to improve health and wellbeing outcomes for Aboriginal families.

# CELL BIOLOGY

## Overview

Our central research theme is the basis for resistance versus susceptibility to allergy and asthma, in particular we are seeking to elucidate the mechanisms that drive these diseases during their very early stages. The long-term goal is to utilize this information to guide the development of preventative treatments for asthma for use in early childhood, before the disease consolidates into its persistent form. In addition, we have developed a specific focus on the mechanisms responsible for triggering acute severe asthma attacks in children with established atopic asthma, in particular how virus infections harness allergic responses to aid them in escaping antimicrobial defenses, and in doing so markedly increase the intensity of airways inflammation and associated symptoms. We are also continuing our research in areas related to pediatric vaccines and immune enhancers, particularly those which increase resistance to respiratory infections. A unifying theme in this research stems from our earlier findings that risk for development of allergy, respiratory infections and asthma is determined primarily by factors that control the functional maturation of the immune system during early childhood. In particular we have shown that a variety of the cellular immune effector mechanisms which are suppressed *in utero* in order to protect the placenta from inflammatory damage are vital for protection against both infections and allergy during infancy, and the functional maturation of these immune mechanisms during the preschool years is sluggish in children from families with a history of allergic diseases. An important complementary stream of research in our Division involves animal model studies

on immunoregulation of the cell populations responsible for triggering T-lymphocyte activation in the airway mucosa during the “late phase response” in asthma. The main focus of this aspect of our research is on interactions between T-regulatory cells and the network of airway mucosal Dendritic Cells discovered earlier by our group, and now acknowledged to be primarily responsible for immune surveillance in the respiratory tract. We have also expanded this experimental area to encompass viral infections and how these interact with and exploit allergic inflammatory mechanisms to evade immune defenses. In addition, we have developed a network of national and international collaborators to translate some of the key findings from this research, into clinical settings. During 2012 our ongoing research projects fell under three overlapping themes, and a summary of the status of these projects, including where applicable a synopsis of key publications arising from these studies, are shown below.

## Aetiology and pathogenesis of atopy and asthma in children

### PERSISTENT EFFECTS OF MATERNAL SMOKING DURING PREGNANCY ON LUNG FUNCTION AND ASTHMA IN ADOLESCENTS

<sup>A</sup>HOLLAMS EM, <sup>DE</sup> <sup>B</sup>KLERK N, <sup>A</sup>HOLT PG, <sup>C</sup>SLY PD.

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<sup>C</sup>QUEENSLAND CHILDREN'S MEDICAL RESEARCH INSTITUTE, THE UNIVERSITY OF QUEENSLAND, BRISBANE.

There is a great deal of evidence that maternal smoking during pregnancy (MSP) has lasting detrimental effects on the health of offspring, including increased body mass index (BMI), decreased lung function and increased risk for development of asthma and wheeze. However, how long these effects persist and how they are mediated is not clearly understood. Impaired immune function has been proposed as a mechanism leading to respiratory disease in children exposed to maternal smoking *in utero*; we explored this possibility using immune function data we compiled during the 14-year-old follow-up of the W.A. Pregnancy Cohort, better known as the Raine Study Cohort. We examined whether maternal smoking in pregnancy: 1) increases risk of respiratory disorders in adolescence via altered immune function; 2) modifies risk of allergic sensitization and related disorders. Data on spirometry, bronchial responsiveness, respiratory symptoms, total and allergen-specific IgE and IgG4, immune function and inflammatory markers were obtained from 1129 participants in and related to maternal smoking in pregnancy and other tobacco smoke exposure using regression analyses. Maternal smoking in pregnancy in the Raine Cohort was associated with low lung function and increased body mass index, in addition to increased risk of asthma and wheezing at age 14; these risks were further increase by continuing exposure to tobacco smoke in childhood. However, maternal smoking in pregnancy was not associated with overall dampening of immune responses at age 14, and it also did not alter risk for developing

allergy. We conclude that maternal smoking in pregnancy increases risk of asthma and wheezing in adolescence via mechanisms including low lung function but not immune impairment.

### INVESTIGATING RELATIONSHIPS BETWEEN VITAMIN D STATUS AND ASTHMA AND ALLERGY DEVELOPMENT THROUGHOUT CHILDHOOD.

<sup>A</sup>HOLLAMS EM, <sup>B</sup>HART PH, <sup>C</sup>ZHANG G, <sup>A</sup>HOLT BJ, <sup>D</sup>SLY PD, <sup>A</sup>HOLT PG.

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Vitamin D has long been associated with bone health, but it also plays an important role in immune regulation and is necessary for development of healthy lung function. Experts have suggested that a lack of vitamin D may be a factor contributing to the surge of asthma rates in recent decades. Vitamin D inadequacy is common, including in Australian children, but disparate findings from cohort studies have had a polarising effect on the scientific community regarding the wisdom of advocating vitamin D supplementation for protection against asthma and allergic disease. We recently measured 25(OH)-vitamin D (the storage form of vitamin D) in blood collected at ages 6 and/or 14 years from



Perth children from the Raine Study Cohort; this measurement included 1380 14-year-olds, 989 6-year-olds, and 689 participants at both ages. In summer 20% of 14-year-olds had what is considered inadequate vitamin D levels, and this percentage rose to 60% in winter. At age 6 increased vitamin D levels were associated with reduced risk of current allergy, predominantly in boys; similar cross-sectional associations were seen at age 14. We found that low vitamin D levels at age 6 predicted development of asthma and/or allergy by age 14. (*Eur Resp J 2011; 38:1320-7*).

Dr Hollams and colleagues have received funding from Asthma Australia to test the hypothesis that inadequate Vitamin D during infancy promotes asthma development by increasing susceptibility to severe respiratory infection and allergic sensitisation. We will utilise the Perth Childhood Asthma Study (CAS) cohort, which is the most intensively studied birth cohort published to date focussing specifically on asthma. The CAS cohort was selected to be at high risk for asthma and allergic disease due to a positive parental history of allergy or asthma, and participants have been followed from birth to age 10 years, including direct physician assessment of all respiratory infections up to age 5. We are in the process of measuring 25(OH)-vitamin D levels from a total of 1673 plasma samples collected at birth and, from samples collected at ages 0.5, 1, 2, 3, 4, 5 & 10 years. This study will potentially be the first in the world to track vitamin D levels from birth throughout childhood, and to relate them to risk for infection, allergy and asthma development.

1. Hollams EM\*, Hart PH\*, Holt BJ, Serralha M, Parsons F, de Klerk NH, Zhang G, Sly

PD, Holt PG. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *Eur Respir J 2011; 38:1320-7*. \*co-first authors

### CHARACTERISATION OF NASOPHARYNGEAL MICROBIAL POPULATIONS IN CHILDREN AT HIGH RISK OF ASTHMA AND ALLERGY USING BACTERIAL METAGENOMICS

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Recent data have shown that normal human lungs contain a rich and phylogenetically diverse population of microbial communities. Interestingly however, colonization of specific bacteria in the hypopharynx of neonates has been implicated as a risk factor for the development of asthma early in life. We initiated a metagenomic assessment of the upper respiratory tract through post-nasal aspirate samples, obtained from individuals recruited in the Perth-based Childhood Asthma Study (CAS) birth cohort. This cohort consists of children at high-risk for asthma and allergy due to parental history of allergy. The pilot analysis of samples taken from 187 infants at 3-6 months of age

with no symptoms of respiratory infection detected 191 bacterial genera, using the Roche 454 GS FLX Titanium sequencer. We previously endeavoured to validate these findings by re-sequencing using the Ion Torrent sequencer, but this was not conclusive due to limitations with discriminating power on the readouts to resolve bacterial genera and species using this platform. We therefore re-extracted bacterial genomic DNA (gDNA) from these individuals when they were asymptomatic of disease and PCR amplicons were generated for 454 sequencing. Additionally, using CAS individuals in the same age group, we extracted bacterial gDNA from nasal aspirate samples taken at the time of a respiratory infection and PCR amplicons for 16S gDNA have been sequenced on the same platform. The analysis of bacterial populations in these initial two groups is ongoing.

### DEVELOPMENTAL-ASSOCIATED DYSREGULATION OF INNATE ANTI-MICROBIAL IMMUNITY IN EARLY LIFE AS A DETERMINANT OF SUSCEPTIBILITY TO ATOPIC ASTHMA

HOLT PG, MOK D, BOSCO A, HOLLAMS EM TELETHON INSTITUTE FOR CHILD HEALTH RESEARCH, CENTRE FOR CHILD HEALTH RESEARCH, THE UNIVERSITY OF WESTERN AUSTRALIA

Forerunner studies from our laboratories have established that the children most likely to develop persistent asthma are those who experience repeated/intense lower respiratory tract infections (LRIs) during infancy, especially if they also show early signs of atopy. The marker for asthma risk in these children is not simply overall infection frequency, but rather

the severity of the accompanying inflammation-associated respiratory symptoms. This suggests that their anti-microbial responses are dysregulated to the extent that they contribute directly to airway tissue damage. Findings in the Childhood Asthma Study (CAS) birth cohort indicate that the most asthmagenic infant LRIs are those associated with fever, a classical marker of acute inflammation and a specific marker of the underlying activation of the inflammasome complex which mediates production of the active forms of pro-inflammatory IL-1-family cytokines. This project will focus on cell populations within the innate arm of the immune system that mediates initial defence against respiratory pathogens, including detailed assessment of inflammasome-associated functions resulting in secretion of pro-inflammatory cytokines. Our core hypothesis is that children at maximum risk of developing persistent asthma are those in whom postnatal maturation of innate immune functions are developmentally delayed, leading to transient dysregulation of their antimicrobial defence mechanisms during infancy. We are testing this hypothesis in cross sectional and prospective studies on cryobanked mononuclear cells from the CAS cohort, examining age-associated changes in regulation of inflammasome-associated functions and relating these to LRI history and subsequent asthma development. One hundred and sixty cord blood samples from this cohort are currently being examined for IL-1 responses, as well as additional inflammatory and regulatory cytokine outputs upon activation with innate stimuli (LPS and poly(I:C)) that have been shown by us to up-regulate and secrete IL-1. These cultures are performed over time to measure both the peak and persistence of the

## ANTI-BACTERIAL ANTIBODY RESPONSES ASSOCIATED WITH THE DEVELOPMENT OF ASTHMA IN ATOPIC AND NON-ATOPIC CHILDREN

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Infants who develop house dust mite (HDM) allergy and children with severe persistent asthma have low antibody responses to the P6 antigen of *Haemophilus influenzae* which is a common respiratory pathogen. As a followup to these observations, we have extended the study to measure the development of antibody to two ubiquitous bacteria strains commonly found on the respiratory mucosa, in a prospective birth cohort at high risk of allergic disease (our CAS cohort), and assessed which responses were associated with asthma and atopy. IgG1 and IgG4 antibody to *H. influenzae* (P4 and P6) and *Streptococcus pneumoniae* (PspA and PspC) surface antigens was measured in yearly blood samples collected from these children up to age 5 years. IgE to the P6 antigen was also examined for the 5-year group. The children were stratified based on HDM sensitization and asthma at 5 years of age. HDM-sensitized children had early impaired IgG1 antibody responses to all the protective bacterial surface antigens. Low

IgG1 titres to the *H. influenzae* antigens were associated with asthma. The IgG4 antibody titre and prevalence were similar in both atopic and non-atopic groups, however atopic children had a slower down-regulation of the IgG4 response. Children with asthma had lower anti-P6 IgE responses. (*Thorax* 2012; 67:321-327).

## FEBRILE RESPIRATORY ILLNESSES IN INFANCY AND ATOPY AS RISK FACTORS FOR PERSISTENT ASTHMA & WHEEZE

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Severe viral respiratory illnesses and atopy are risk factors for childhood wheezing and asthma. The aim of this study was to explore associations between severe respiratory infections and atopy in early childhood with wheeze and asthma persisting into later childhood. 147 children at high atopic risk (our CAS cohort) were followed from birth to age 10 yrs. Data on all respiratory infections occurring in infancy were collected prospectively and viral aetiology ascertained. Atopy was measured by skin prick tests at 6 months, and 2 and 5 yrs. History of wheeze and doctor diagnosed eczema and asthma was collected regularly until 10 yrs of age. At 10

yrs, 60% of the cohort was atopic, 25.9% had current eczema, 18.4% current asthma and 20.4% persistent wheeze. 35.8% experienced at least one lower respiratory infection (LRI) associated with fever and/or wheeze in first year of life. Children who had wheezy or, in particular, febrile LRI in infancy and were atopic by 2 yrs, were significantly more likely to have persistent wheeze (RR 3.51, 95% CI 1.83–6.70; p,0.001) and current asthma (RR 4.92, 95% CI 2.59–9.36; p,0.001) at 10 yrs. Severe viral respiratory infections in infancy and early atopy are risk factors for persistent wheeze and asthma. The strongest marker of the asthmatogenic potential of early life infections was concurrent fever. The occurrence of fever during respiratory illnesses is an important marker of risk for wheeze and asthma later in childhood, suggesting it should be measured in prospective studies of asthma aetiology. (*European Respiratory Journal* 2012; 39:876-882).

## INFECTIONS AND ATOPY IN ASTHMA PATHOGENESIS: NEW RATIONALES FOR ASTHMA PREVENTION AND TREATMENT

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Prospective birth cohort studies tracking asthma initiation and consolidation in community cohorts have identified viral infections occurring against a background of allergic sensitization to

aeroallergens as a uniquely potent risk factor for the expression of acute severe asthma-like symptoms and for the ensuing development of asthma that can persist through childhood and into adulthood. A combination of recent experimental and human studies including a series from our group and our collaborators, have suggested that underlying this bipartite process are a series of interactions between antiviral and atopic inflammatory pathways that are mediated by local activation of myeloid cell populations in the airway mucosa, and the parallel programming and recruitment of their replacements from bone marrow. Targeting key components of these pathways at the appropriate stages of asthma provides new opportunities for the treatment of established asthma but, more crucially, for primary and secondary prevention of asthma during childhood. We have integrated these potential treatment strategies into a “template” for the design of clinical trials, some of which are already in the process of being implemented, and the scientific rationale for this approach is discussed in detail. (*Nature Medicine* 2012; 18:726-735).

## AIRWAY EPITHELIAL CELLS CONDITION DENDRITIC CELLS TO EXPRESS MULTIPLE IMMUNE SURVEILLANCE GENES

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Increasing evidence suggests that crosstalk between airway epithelial cells (AEC) and adjacent dendritic cells (DC) tightly regulates airway mucosal DC function in steady state. AEC are known to express multiple immunomodulatory factors, though detailed information on how this influences human DC function remains incomplete. We recently demonstrated using an *in vitro* coculture model that AEC alter differentiation of monocytes into DC in a manner that inhibits expression of potentially damaging Th2 effector function. In this current study, we extended these findings to examine other aspects of DC function. Using microarray technology we showed that multiple genes important for immune surveillance are significantly over expressed in purified AEC-conditioned DC, compared to control DC. These findings were confirmed by quantitative real time PCR or flow cytometry in an independent sample set. In particular, AEC-conditioned DC showed selective upregulation of chemokines that recruit Th1 cells, but minimal change in chemokines linked to Th2 cell recruitment. AEC-conditioned DC were also characterized by enhanced expression of complement family genes (C1QB, C2, CD59 and SERPING1), Fcγ receptor genes (FCGR1A, FCGR2A, FCGR2B and FCGR2C), signaling lymphocytic activation molecule family member 1 (SLAMF), programmed death ligands 1 and 2, CD54 and CD200R1, relative to control DC. These findings suggest that AEC conditioning facilitates the capacity of DC to react to danger signals, to enhance leukocyte recruitment, especially of Th1 effector cells, and to interact with other immune cell populations while minimizing the risks of excessive inflammation leading to tissue

damage. (*PLoS One* 2102; 7(9) e44941 doi: 10.1371/journal.pone.0044941).

## META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES IDENTIFIES THREE NEW RISK LOCI FOR ATOPIC DERMATITIS

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Atopic dermatitis (AD) is a commonly occurring chronic skin disease with high heritability. Apart from filaggrin (*FLG*), the genes influencing atopic dermatitis are largely unknown. We contributed data on AD collected from our 14 year followup of the RAINE study cohort to a multicenter collaboration with the Early Genetics & Lifecourse Epidemiology (EAGLE) Consortium, with involved a genome-wide association meta-analysis of 5,606 affected individuals and 20,565 controls from a total of 16 population based cohorts. This was followed by examination of the ten most strongly associated new susceptibility loci in an additional 5,419 affected individuals and 19,833 controls from 14 studies. Three SNPs reached genome-wide significance in the discovery and replication cohorts combined, including rs479844 upstream of *OVOL1* (odds ratio (OR) = 0.88,  $P = 1.1$

$\times 10^{-13}$ ) and rs2164983 near *ACTL9* (OR = 1.16,  $P = 7.1 \times 10^{-9}$ ), both of which are near genes that have been implicated in epidermal proliferation and differentiation, as well as rs2897442 in *KIF3A* within the cytokine cluster at 5q31.1 (OR = 1.11,  $P = 3.8 \times 10^{-8}$ ). We also replicated association with the *FLG* locus and with two recently identified association signals at 11q13.5 (rs7927894;  $P = 0.008$ ) and 20q13.33 (rs6010620;  $P = 0.002$ ). The results underline the importance of both epidermal barrier function and immune dysregulation in atopic dermatitis pathogenesis. (*Nature Genetics* 2012; 44; 187-192).

## INTERFERON REGULATORY FACTOR 7 IS A MAJOR HUB CONNECTING INTERFERON-MEDIATED RESPONSES IN VIRUS-INDUCED ASTHMA EXACERBATIONS IN VIVO.

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Exacerbations are responsible for a substantial burden of morbidity and health care use in children with asthma. Most asthma exacerbations are triggered by viral infections; however, the underlying mechanisms have not been systematically investigated. The objective of this study was to elucidate the molecular networks that underpin virus-induced exacerbations in asthmatic children in vivo. We followed exacerbation-prone asthmatic

children prospectively and profiled global patterns of gene expression in nasal lavage samples obtained during an acute, moderate, picornavirus-induced exacerbation and 7 to 14 days later. Coexpression network analysis and prior knowledge was used to reconstruct the underlying gene networks. The data showed that an intricate modular program consisting of more than 1000 genes was upregulated during acute exacerbations in comparison with 7 to 14 days later. The modules were enriched for coherent cellular processes, including interferon-induced antiviral responses, innate pathogen sensing, response to wounding, small nucleolar RNAs, and the ubiquitin-proteasome and lysosome degradation pathways. Reconstruction of the wiring diagram of the modules revealed the presence of hyperconnected hub nodes, most notably interferon regulatory factor 7, which was identified as a major hub linking interferon-mediated antiviral responses. This study provides an integrated view of the inflammatory networks that are upregulated during virus-induced asthma exacerbations in vivo. A series of innate signaling hubs were identified that could be novel therapeutic targets for asthma attacks.

## Pediatric Vaccine Studies

### EFFECT OF EARLY CARRIAGE OF STREPTOCOCCUS PNEUMONIAE ON THE DEVELOPMENT OF PNEUMOCOCCAL PROTEIN-SPECIFIC CELLULAR IMMUNE RESPONSES IN INFANCY

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The aim of this study was to examine the relationship between nasopharyngeal pneumococcal colonization in early life and the subsequent development of pneumococcal-specific T cell responses. Prenasal swabs were collected from Papua New Guinean infants 1 and 2 weeks after birth (n = 279). At 9 months in vitro cellular immune responses to choline binding protein A (n = 132), pneumococcal surface protein A (n = 132), pneumolysin (n = 99) and the pneumococcal conjugate vaccine carrier CRM were determined. Responses were compared based on the children's carriage status within the first 2 weeks of life. Within the first two weeks of life, 40% of the study children had carried *Streptococcus pneumoniae*. Early carriage was associated with lower interferon-γ and interleukin 10 responses to pneumococcal

proteins at age 9 months when children had not received pneumococcal conjugate vaccines during the study period. We conclude that early pneumococcal carriage may result in enhanced disease susceptibility and suboptimal vaccine responses by modulating the development of pneumococcal immune responses. (*Pediatric Infectious Diseases Journal* 2012; 31(3) 243-248).

## A GENOMICS-BASED APPROACH TO ASSESSMENT OF VACCINE SAFETY AND IMMUNOGENICITY IN CHILDREN

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Immune responses to vaccines in infants and young children are typically Th2-biased, giving rise to concerns regarding potential atopy-like side effects, and antagonism of Th1-associated sterilising immunity. Conventional immunological methodology has limited capacity to effectively address these problems because of the inherent complexity of the immune responses involved. To address this deficiency, we have sought to develop an unbiased systems biology approach to elucidate superficially similar Th2-associated responses to paediatric vaccines and allergens, and to differentiate between them via gene coexpression network analysis. We have demonstrated that in immune responses to the diphtheria/acellular pertussis/

tetanus and pneumococcal polysaccharide conjugate vaccines, potentially antagonistic Th1-/IFN-associated and Th2-associated gene networks coexist in an apparent state of dynamic equilibrium, whereas in Th2-dominant allergen-specific responses of atopics the Th1 and IFN networks are respectively disrupted and downregulated. Capacity to detect and interpret these covert differences between responses to vaccines and allergens relies on the use of sophisticated algorithms that underpin coexpression network analysis, which identify genes that function co-ordinately in complex pathways. This methodology has significant potential to identify covert interactions between inflammatory pathways triggered by vaccination, and as such may be a useful tool in prediction of vaccine safety/efficacy. (*Vaccine* 2012; 30:1865-1874).

## ONTOGENY OF TOLL-LIKE AND NOD-LIKE RECEPTOR-MEDIATED INNATE IMMUNE RESPONSES IN PAPUA NEW GUINEAN INFANTS

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Studies addressing the ontogeny of the innate immune system in early life have reported

mainly on Toll-like receptor (TLR) responses in infants living in high-income countries, with little or even no information on other pattern recognition receptors or on early life innate immune responses in children living under very different environmental conditions in less developed parts of the world. In this study, we described whole blood innate immune responses to both Toll-like and nucleotide-binding oligomerization domain (NOD)-like receptor agonists including the widely used vaccine adjuvant 'alum' in a group of Papua New Guinean infants aged 1–3 (n = 18), 4–6 (n = 18), 7–12 (n = 21) and 13–18 (n = 10) months old. Depending on the ligands and cytokines studied, different age-related patterns were found: alum-induced IL-1b and CXCL8 responses were found to significantly decline with increasing age; inflammatory (IL-6, IL-1b, IFN-γ) responses to TLR2 and TLR3 agonists increased; and IL-10 responses remained constant or increased during infancy, while TNF-α responses either declined or remained the same. We report for the first time that whole blood innate immune responses to the vaccine adjuvant alum decrease with age in infancy; a finding that may imply that the adjuvant effect of alum in pediatric vaccines could be age-related. Our findings further suggest that patterns of innate immune development may vary between geographically diverse populations, which in line with the 'hygiene hypothesis' particularly involves persistence of innate IL-10 responses in populations experiencing higher infectious pressure. (*PLoS One* 2012; 7(5) e36793 doi 10.1371/journal.pone.0036793).

## NEONATAL ANTIGEN PRESENTING

## CELLS ARE FUNCTIONALLY MORE QUIESCENT IN CHILDREN BORN UNDER TRADITIONAL COMPARED TO MODERN ENVIRONMENTAL CONDITIONS

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One explanation for the high burden of allergic and autoimmune diseases in industrialized countries is inappropriate immune development under modern environmental conditions. There is increasing evidence that the process of immune deviation already begins in utero, but the underlying immunologic mechanisms are not clear. We sought to identify differences in the function of neonatal antigen-presenting cells (APCs) in children born in settings that are more traditional versus those of modern societies. Cord blood mononuclear cells were collected from newborns from Papua New Guinea (PNG; traditional) and Australia (modern) and compared for differences in APCs and T-cell phenotype and function. Australian cord naive T cells (CD4+CD25-CD127+ cells) showed an enhanced and more rapid proliferative response in an autologous, APC-dependent culture system, a result of differences in neonatal APCs rather than T-cell function. This included an increased capacity to process antigen and to upregulate activation markers after stimulation. In contrast, resting PNG APCs

exhibited higher baseline levels of activation and inhibitory markers and were less responsive or nonresponsive to stimulation *in vitro*. (*J Allergy & Clin Immunol* 2012; 130(5) 1167-1174).

## Animal Model Studies

### DEFECTIVE AEROALLERGEN SURVEILLANCE BY AIRWAY MUCOSAL DENDRITIC CELLS AS A DETERMINANT OF RISK FOR PERSISTENT AIRWAYS HYPER-RESPONSIVENESS IN EXPERIMENTAL ASTHMA

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A hallmark of atopic asthma is development of chronic airways hyper-responsiveness (AHR) that persists in the face of ongoing exposure to perennial aeroallergens. We investigated underlying mechanisms in sensitized rats focusing on a strain expressing the high-allergen – responder phenotype characteristic of human atopic asthmatics, and find that their high susceptibility to aeroallergen-induced persistent AHR is associated with deficiencies in the immunoregulatory and mucosal trafficking properties of inducible T-regulatory cells (iTregs). Counterintuitively, AHR susceptibility was inversely related to

aeroallergen exposure level, high exposures conferring protection. We demonstrated that underlying this AHR-susceptible phenotype was reduced capacity of airway mucosal dendritic cells (AMDCs) for allergen sampling *in vivo*; this defect is microenvironmentally acquired, as allergen uptake by these cells *in vitro* is normal. Moreover, intranasal transfer of *in vitro* aeroallergen-loaded AMDC from naïve animals into AHR-susceptible animals during prolonged aerosol challenge markedly boosts subsequent accumulation of iTregs in the airway mucosa and rapidly resolves their chronic AHR, suggesting that compromised antigen surveillance by AMDC resulting in defective functional programming of iTreg may be causally related to AHR susceptibility. (*Mucosal Immunol.* 2012; 5(3):332-341)

### RESPIRATORY VIRAL INFECTIONS AS TRIGGERS OF ACUTE SEVERE ASTHMA EXACERBATIONS IN ATOPICS: MECHANISTIC STUDIES IN AN EXPERIMENTAL MODEL

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One of the most active areas of asthma research relates to the role of viral infections in the disease process, particularly in relation to atopic asthmatics in whom Th2-associated responses to aeroallergens is perceived to be a key factor in precipitating the disease. There is strong epidemiological evidence implicating inhalant allergy as a potent asthma risk factor in children and young adults, however several

large studies including our own have shown that whilst the vast majority of young asthmatics are atopic only a minority (<20%) of atopics develop asthma, suggesting that additional cofactors are required to drive disease pathogenesis. Respiratory viral infections have been identified as prime candidates for such a cofactor role in atopic asthma, and these can operate in susceptible subjects independently of atopy and/or can apparently interact synergistically with the effects of atopy to maximise asthma risk. These and related findings have provoked considerable controversy, including claims of “reverse causality” i.e. that the atopic state may itself predispose to viral infections in the airways and that this may be sufficient to explain the association. Our own recent findings suggest that the connection between atopy and infection in this context may be more intimate. This project includes a series of mechanistic studies to investigate the effects of respiratory viral infection in an established rat atopic asthma model that mimics essential characteristics of the human disease. We have established the model for viral infection in rat strains expressing high (HR) versus low (LR) IgE responder phenotype, using a Rhinovirus (RV) adapted to infect rats, to best compliment the findings in humans that have shown strong associations between RV infection and acute asthma exacerbation in children. We are documenting the inflammatory response to viral infection following a time course post infection in male and female HR and LR rat strains, including viral titre, airways inflammation, cytokine production and cellular immunology profiles of T cell and DC subsets. In parallel, we are overlaying viral infection onto previously sensitized rats, and then following aerosol exposure of virally

infected rats to the sensitizing allergen we are investigating how allergic responses interplay with existing viral infection to influence local Th2 (allergic) immune responses to aeroallergen challenge in the airway mucosa, thereby increasing the intensity of acute inflammation and the duration of ensuing airways hyperresponsiveness (AHR).

### LONG-TERM DERANGEMENT OF ANTIGEN PRESENTING CELL POPULATIONS IN THE RESPIRATORY TRACT FOLLOWING INFLUENZA A INFECTION

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Inhaled environmental antigens pose a major challenge to the maintenance of immunological homeostasis in the respiratory tract (RT), requiring screening for their potential danger to the host and ignored if harmless or rapidly neutralised if dangerous. This requires a balanced network of antigen presenting cells (APC) that can regulate tolerance or immunity as required. Influenza virus poses a serious threat of long-term disruption of this balance via its potent inflammatory and cytotoxic activities, potentially increasing the risk of allergic sensitisation or decreasing resistance to secondary infections. In these studies, we have utilised a mouse model of H1N1 Influenza

Type A Virus (IAV) infection to examine the dynamics and activation states of APC in airway mucosal (AM) and parenchymal lung (PL) tissue of the RT during and following IAV infection. In adult mice, we found marked differences in the depletion and reconstitution of dendritic cells (DC) subsets in the AM and PL environments, with a generally more acute responses in AM DC that resolved by day 7 after infection, but with persistent depletion of PL DC for up to 3 weeks following infection. Similarly, transient activation of AM DC was seen at day 7 after infection, but this was delayed until day 14 in PL DC. A striking depletion of tissue-resident PL macrophages was observed at day 14 post-infection, a week after viral clearance, with these cells showing a persistent activation state. Finally, in mice infected at 3 weeks of age, PL DC and macrophages showed persistent changes for up to 5 weeks following IAV infection. These data demonstrate that IAV has differential effects on APC populations in compartments of the RT, leading to long-term derangement in the numbers and activation states of these cells, that may disrupt the fine balance of immunological protection in this environment.

### ROLE OF CD103 IN THE REGULATION OF IMMUNITY TO INHALED ALLERGENS

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CD103 is the  $\alpha$  chain of integrin  $\alpha$ E $\beta$ 7, an

adhesion molecule that mediates cell binding to epithelial cells via E-cadherin. This molecule is expressed by subsets of dendritic cells and T cells, and is important in T cell homing to epithelial barriers and marks a subset of dendritic cells that can mediate tolerogenic T cell responses to environmental allergens. In these studies we are examining the role of CD103 in the development of allergic asthma using mouse models of sensitization followed by inhaled-allergen challenge to induce allergic airways disease. CD103 knock-out (CD103<sup>-/-</sup>) mice developed a range of hallmark features of atopy and allergy, including OVA-specific IgE and elevated eosinophils in bronchoalveolar washings, although these were markedly elevated compared to sensitized and challenged wild type mice. Inhaled allergen capture and trafficking by dendritic cell subsets in the airways of CD103<sup>-/-</sup> mice was also altered, as well the generation and trafficking to the lungs of allergen-induced effector, memory and regulatory T cell subsets when compared to wild-type mice, with preliminary studies also suggesting that CD103<sup>-/-</sup> mice show modified lung physiological responses to methacholine following allergen challenge. These data suggest a pivotal role for CD103 in the early stages of systemic allergic sensitization and generation of allergen-specific IgE, as well as at later stages in the initiation and regulation of the local lung immune responses to allergen rechallenge.

### MECHANISMS OF IGE SENSITIZATION

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A key risk factor that has been identified in association with the rising prevalence of allergic asthma is an increase in atopic (IgE mediated) sensitization to aeroallergens. To date, there has been limited progress in dissecting the nature of the antecedent immunological mechanisms that underlie generation of mucosal IgE sensitization, as opposed to the normal response of protective tolerance to aeroallergens. The induction of "mucosal tolerance" to aeroallergen, initially described and characterised in animal model studies from our laboratory, represents one of the established paradigms in lung immunology. Selective attenuation of Th2 skewed immunity, particularly production of IgE, can be attained by repeated exposure via the respiratory route. This was associated with induction of a phenotypically heterogeneous population of T cells with "regulatory" activity. Of note, induction of tolerance in animals that are hyper-susceptible to allergic disease and develop high IgE responses (high responder; HR) required log fold higher levels of exposure to OVA than their low-responder (LR) counterparts or dust mite allergen. No satisfactory explanation exists to explain this profound difference in efficiency of mucosal tolerance mechanisms. This study derives from recent novel and counterintuitive epidemiological findings suggesting that risk for IgE sensitization to inhalant allergens may be inversely related to allergen exposure levels. Our core hypothesis is that variations in the functional capacity of respiratory immune cell surveillance mechanisms results in a spectrum of susceptibility to development of protective

IgE tolerance to aeroallergens, and our HR/LR rat model provides unique opportunities to systematically test that hypothesis. Our preliminary studies align well with our core hypotheses and suggest that in LR rats, intranasal exposure to daily high dose antigen results in earlier development of IgE tolerance and that this is associated with earlier increased induction of iTreg in the DLN.

## DIFFERENTIAL ACTIVITY OF TYPE I INTERFERONS ON AIRWAYS RESPONSE TO ALLERGEN.

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Asthma is a significant and increasing health burden, impacting on personal quality of life, lost work productivity and the health service. Recent studies implicate early life respiratory viral infection and concomitant IgE sensitisation to allergen as strong risk factors in the development of atopic asthma. One hypothesis is that signals elicited in response to respiratory viral infection cross stimulate responses to allergen, leading to sensitization and subsequent allergic asthmatic responses. The early innate immune response to respiratory viral infection is high level Type I IFN production from dendritic cells and airway epithelial cells. Therefore, this family of cytokines may potentially play a key role in the viral induction of inappropriate responses to airway allergen, which contribute to the development of asthma. Two key cell

types involved in the development, progression and resolution of allergic asthma exacerbations include airway mucosal DCs and T regulatory cells. This project examines the effect of IFN $\alpha$ 2 and IFN $\alpha$  intranasal delivery on airway dendritic cells, T cells and T regulatory cells. We demonstrate the influence of IFN $\alpha$ 2 and IFN $\alpha$  intranasal delivery on the development of sensitization and/or tolerance to allergen.

## Staff and Students

### HEAD OF DIVISION

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### VISITING RESEARCH FELLOWS

Dr Karen Schuepp MD, University Children's Hospital, Bern, Switzerland.

## External Committees

### INTERNATIONAL

Patrick Holt. NIH Expert Committee on Immunotherapy.

Patrick Holt. NIH Expert Committee: Development of strategies for asthma prevention

Patrick Holt. NIH Program Grant advisory panel - URECA study, University of Wisconsin.

Patrick Holt. International Scientific Advisory Board, Centre for Translational Medicine, James Connolly Memorial Hospital, Dublin.

Patrick Holt. NIH Project Grant advisory panel – Precursors of Food Allergy in Newborns, Children's Memorial Hospital, Chicago.

Deborah Strickland. Asthma UK

Deborah Strickland. Netherlands Asthma Foundation.

## Presentations 2012

Patrick G. Holt, Symposium Speaker: The ontogeny of the allergic phenotype – EAACI Congress, Geneva.

Patrick G. Holt, Symposium Speaker: Primary prevention of allergic disease – Symposium on Specific Allergy, Berlin.

Patrick G. Holt, Plenary Speaker: Predicting the effects of vaccination in atopic children – International Alliance for Biological Standardization Conference “Biomarkers of Inflammation”, Baltimore.

Patrick G. Holt, Workshop Speaker: Why/When/How to assess atopy-associated risk during vaccine development - International Alliance for Biological Standardization Conference “Biomarkers of Inflammation”, Baltimore.

Patrick G. Holt, Workshop Seminar: Unresolved issues relating to risk for development of asthma in childhood – NIH International Workshop on Asthma Birth Cohorts, Bethesda.

Patrick G. Holt, Plenary Speaker: Aetiology and pathogenesis of atopic asthma: insights from childhood cohort studies – Annual Meeting of Japanese Society for Allergology, Osaka.

Patrick G. Holt, Symposium Speaker: Primary and secondary prevention strategies for atopic asthma: new rationales - Annual Meeting of Japanese Society for Allergology, Osaka.

Patrick G. Holt, Invited seminar: Strategic targets for asthma prevention - GlaxoSmithKline, Stevenage.

Patrick G. Holt, Invited seminar: Asthma pathogenesis in children - Johns Hopkins University, School of Public Health, Baltimore.

Deborah H. Strickland, American Thoracic Society, Symposium speaker, San Francisco, USA, May 2012.

## ACTIVE collaborations

Fernando Martinez, Respiratory Sciences Center, University of Arizona, USA

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# LEUKAEMIA AND CANCER RESEARCH

## Overview

Cancers in children comprise many different diseases. More than half of them affect cells of the immune system and the central nervous system, while only a minority are carcinomas, contrasting with cancer diagnoses in adults. Hence, the most common malignancy in children is leukaemia, followed by brain tumours. Despite marked improvements in the cure rates for paediatric cancers, leukaemias and brain tumours account for half of the deaths. In order to find better therapies for children with cancer, our Division at the Institute and the Oncology Total Care Unit at Princess Margaret Hospital (PMH) are both members of the largest study group into these diseases, the US-based Children's Oncology Group (COG). The major goal is to improve our understanding of paediatric cancers and leukaemia, and work towards curative therapy for patients.

The Division focuses on research into childhood leukaemia, brain tumours and a very rare disease in children, undifferentiated carcinoma. The main aims are the identification of genetic alterations that lead to childhood cancers and the application of this knowledge to the prognosis and improved therapeutic approaches for patients. In order to examine the genetic lesions present in the various types of cancer, we make use of microarray and sequencing technologies. Our experimental model systems, including a panel of established leukaemia and cancer cell lines, are ideal tools for testing potential new drugs for the treatment of patients.

## Leukaemia

### ROLE OF MICROENVIRONMENT INTERACTIONS IN CHILDHOOD LEUKAEMIA

JE WELLS, M HOWLETT, J FORD, AL SAMUELS, J HENG, H HALSE AND UR KEES IN COLLABORATION WITH C COLE, HAEMATOLOGY-ONCOLOGY, PRINCESS MARGARET HOSPITAL AND DR BRIGSTOCK, PAEDIATRIC SURGERY RESEARCH LABORATORY, CHILDREN'S RESEARCH INSTITUTE, COLUMBUS, OHIO, USA.

In children with acute lymphoblastic leukaemia (ALL) the bone marrow microenvironment is the site of leukaemic cell proliferation. Recently, the surrounding bone marrow stromal cells have been shown to play a critical role in clinical outcome by affecting leukaemic cell survival and drug resistance. The mechanism by which this stromal protection takes place is unclear. To identify genes and pathways linked to the disease and drug resistance we performed transcriptional profiling of B precursor (pre-B) ALL compared to normal CD34+ cells. We found that connective tissue growth factor (*CTGF*) was overexpressed in 75% of pre-B ALL specimens and showed a 19-fold up-regulation by qRT-PCR versus normal CD34+ cells. Incubation of recombinant human *CTGF* with either a pre-B ALL cell line or a human bone marrow cell line (H55) was examined to monitor effects on proliferation and adhesion. *CTGF* increased proliferation of bone marrow stromal cells yet did not alter the proliferation of pre-B ALL cells. Furthermore, *CTGF* acted on stromal cells to increase adhesion of pre-B ALL cells to the stroma. Microarray gene expression analysis of H55 cells incubated with *CTGF* affected

genes involved in cholesterol and fatty acid metabolism, extracellular matrix production, cell motility and cell cycle. We are currently validating these findings *in vitro* through overexpression of *CTGF* in pre-B ALL cells using stable retroviral transfection. We hypothesise that secretion of *CTGF* initiates a cascade of events, contributing to leukaemogenesis and adhesion-mediated drug resistance. Delineating these events will lead to a better understanding of therapy resistance in children with ALL and strategies for overcoming resistance.

*This work was supported by NHMRC and the Children's Leukaemia and Cancer Research Foundation, WA.*

### HYPOMETHYLATION OF THE CTGF GENE LOCUS IS A COMMON FEATURE OF PAEDIATRIC PRE-B ACUTE LYMPHOBLASTIC LEUKAEMIA

M WELCH AND UR KEES IN COLLABORATION WITH WK GREENE, DIVISION OF HEALTH SCIENCE, MURDOCH UNIVERSITY, PERTH.

Connective tissue growth factor (*CTGF*) is a matricellular protein aberrantly expressed in a high proportion (75%) of B-lineage acute lymphoblastic leukaemias (pre-B ALL) and is associated with poor outcome. We investigated the role of genetic and epigenetic factors leading to *CTGF* expression in paediatric pre-B ALL. Our findings reveal that methylation of the *CTGF* CpG island, rather than gene copy-number changes, translocations or mutations, correlate with expression of *CTGF* in pre-B ALL. The *CTGF* gene contains a dense 5' CpG island (CpGi) and methylation-specific PCR identified an inverse correlation between *CTGF*

gene expression and methylation of the *CTGF* CpGi in pre-B ALL cell lines, and this finding was confirmed using bisulfite sequencing. Culture with 5-aza-2'-deoxycytidine and Trichostatin-A resulted in a significant increase in *CTGF* expression, confirming that global changes in DNA methylation and histone acetylation can influence *CTGF* transcription. Bisulfite sequencing revealed hypomethylation of the *CTGF* locus was a consistent feature of primary B-lineage ALL. By contrast T-ALL specimens, which do not express *CTGF*, were hypermethylated. Bone marrow derived CD34<sup>pos</sup> cells were found to be completely unmethylated at the *CTGF* locus. These findings provide the basis to examine gene-targeted approaches to achieve epigenetic reprogramming of *CTGF* expression in leukaemia.

*This work was supported by the Cancer Council of WA and the Children's Leukaemia and Cancer Research Foundation, WA.*

### IDENTIFYING THE ROLE OF CONNECTIVE TISSUE GROWTH FACTOR (CTGF) IN HAEMATOPOIESIS

CTL CHEUNG AND UR KEES IN COLLABORATION WITH DH STRICKLAND, DIVISION OF CELL BIOLOGY, AND AK CHARLES, PRINCESS MARGARET HOSPITAL, PERTH AND WS ALEXANDER, WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH, MELBOURNE, AND KM LYONS, UCLA, LOS ANGELES, USA.

Connective tissue growth factor (*CTGF*) is a member of the CCN gene family, whose protein products have critical roles in bone formation, and in fibroblasts, chondrocytes and endothelial cells. Our studies showed that *CTGF*

was highly upregulated in acute lymphoblastic leukaemia of pre-B type (pre-B ALL). *CTGF* also plays a role in osteoblast proliferation and differentiation, and these cells are known to control haematopoietic stem cells (HSCs) *via* production of factors essential for renewal and maturation. The balance of HSC self-renewal and differentiation is highly regulated by intrinsic factors together with cues from the surrounding microenvironment, including growth factors. Hence, we hypothesize that *CTGF* plays a role in haematopoiesis. We studied mice with targeted disruption of the *Ctgf* gene. *Ctgf*<sup>-/-</sup> mice die perinatally, owing to respiratory failure. Flow cytometry was used to enumerate the B, T and myeloid populations. *Ctgf*<sup>-/-</sup> neonatal livers were examined, and *Ctgf*<sup>+/-</sup> mice were studied and compared to wild type (WT) at 4 weeks and 8 weeks of age.

Initially we measured the content of B, T and myeloid populations in blood, bone marrow (BM), spleen, thymus and lymph nodes, comparing WT with *Ctgf*<sup>+/-</sup> mice. No significant differences were recorded. Interestingly, the neonatal liver cells of *Ctgf*<sup>-/-</sup> mice showed increased proportions of B cells and a decrease of myeloid cells compared to *Ctgf*<sup>+/-</sup> and WT liver cells. Taken together, we demonstrated that deletion of *Ctgf* influences the balance of B lymphopoiesis and myelopoiesis in mutant neonatal livers. To further examine the role of *CTGF* in HSCs and microenvironment, a series of transplantation experiments are under way; *Ctgf*<sup>-/-</sup> or *Ctgf*<sup>+/-</sup> HSCs are being transplanted into WT mice, to determine the repopulation capacity of cells.

*This work was supported by the Children's Leukaemia and Cancer Research Foundation, WA.*

## DRUG-GENE MODELING IN PAEDIATRIC T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA HIGHLIGHTS IMPORTANCE OF 6-MERCAPTOPYRINE FOR OUTCOME

AH BEESLEY, A SAMUELS, J FORD AND UR KEES IN COLLABORATION WITH D ANDERSON AND MJ FIRTH, DIVISION OF BIOSTATISTICS AND GENETIC EPIDEMIOLOGY.

Children with acute lymphoblastic leukaemia (ALL) are treated with complex chemotherapy regimens of up to ten different drugs according to risk stratification at diagnosis. Around 80% of patients achieve continuous complete remission with early response to drug therapy being one of the strongest predictors of outcome. However, patients relapsing with T-cell ALL (T-ALL) face a dismal outcome. The aim of this study was to identify new markers of drug-resistance and clinical response in T-ALL. We measured gene expression and drug sensitivity in 15 paediatric T-ALL cell lines to find signatures predictive of resistance to ten drugs used in therapy. These were used to generate a model for outcome prediction in patient cohorts using microarray data from diagnosis specimens. In three independent T-ALL cohorts the ten-drug model was able to accurately identify patient outcome, indicating that the *in vitro* derived drug-gene profiles were clinically relevant. Importantly, predictions of outcome within each cohort were linked to distinct drugs, suggesting that different mechanisms contribute to relapse. Sulfite oxidase (*SUOX*) expression and the drug-transporter *ABCC1* (MRP1) were linked to thiopurine sensitivity, suggesting novel pathways for targeting resistance. This study advances our understanding of drug resistance in T-ALL and provides new markers for patient stratification.

The results suggest potential benefit from the earlier use of 6-mercaptopurine in T-ALL therapy or the development of adjuvants that may sensitize blasts to this drug. The methodology developed in this study could be applied to other cancers to achieve patient stratification at the time of diagnosis.

*This work was supported by the Children's Leukaemia and Cancer Research Foundation, WA.*

## WHOLE EXOME SEQUENCE ANALYSIS OF AN IN VITRO MODEL OF DRUG-RESISTANT T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA

MN CRUICKSHANK, J FORD, A GOUT, RS KOTECHA, AH BEESLEY AND UR KEES, IN COLLABORATION WITH R FRANCIS, DIVISION OF BIOINFORMATICS.

The detection of chromosomal abnormalities in childhood leukaemia provides important prognostic markers to guide treatment. Cytogenetic risk stratification for paediatric B-cell acute lymphoblastic leukaemia (ALL) is well established and is essential for selection of therapy. In contrast, genetic alterations predicting response to chemotherapy in paediatric T-cell ALL (T-ALL) require further investigations. We are studying the molecular mechanisms of T-ALL sensitivity and resistance to flavopiridol, a compound belonging to the isoflavone class that is a cyclin-dependent kinase inhibitor (CDK inhibitor). We have found that flavopiridol is highly cytotoxic in T-ALL cell lines. We generated a series of leukaemia cells resistant to flavopiridol by selection of the T-ALL line PER-255 with pulsed high-dose

or continuous low-dose flavopiridol exposure. We isolated clonal populations of flavopiridol-resistant T-ALL cells by limiting dilution and used whole exome sequencing to identify sequence alterations among resistant and sensitive clones. Using Illumina TruSeq™ Exome Enrichment and the HiSeq™ 2000 sequencing platform, we observe 82.3-83.5% of reads aligning to targeted genomic sequence (n=4 resistant PER-255; n=2 sensitive PER-255) with mean coverage range of 59-69.

Exonic, non-synonymous single nucleotide variants (SNVs) were filtered to identify those with at least five identical non-reference genotypes from at least 20 total reads. Comparison of CDK inhibitor-resistant and control exome-seq data identified 629 common SNVs among resistant clones that were absent in parental T-ALL cells. Of these drug-resistant associated variants, 30 were predicted to result in a potentially damaging mutation assessed by PolyPhen 2. Three such variants were novel mutations at three gene loci: a circadian pattern regulator (*PER2*: period circadian clock 2), a phosphoinositide regulator (*SNX2*: sorting nexin 2) and a guanosine Wybutosine regulator (*LCMT2*; leucine carboxyl methyltransferase 2). Interestingly, we also found a predicted deleterious variant in a gene encoding a UDP-glucuronosyltransferase (*UGT1A8*), involved in the metabolism of isoflavones and steroids. These metabolic regulators may represent novel therapeutic targets for drug-resistant T-ALL. Further studies to explore whether these variants arise in T-ALL patients are expected to reveal the clinical relevance of genetic alterations identified in this model system.

*This work was supported by the Children's*

Leukaemia and Cancer Research Foundation, WA.

### MODULATION OF ENERGY METABOLISM PATHWAYS ASSOCIATED WITH GLUCOCORTICOID RESISTANCE IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA (T-ALL)

AL SAMUELS, J HENG, F ONG, AH BEESLEY AND UR KEES IN COLLABORATION WITH KW CARTER AND RW FRANCIS, DIVISION OF BIOSTATISTICS AND BIOINFORMATICS.

Despite significant improvements in the treatment of childhood T-cell acute lymphoblastic leukaemia (T-ALL), up to 30% of patients will relapse and most of those face a dismal prognosis. Resistance to glucocorticoids (GC) is known to be a major factor contributing to the poor prognosis of relapsed ALL, however, it is still unclear how patients develop resistance and which pathways are deregulated. We predict that modulation of glucose metabolism pathways may be associated with drug resistance and evasion of apoptosis. To assess the bioenergetic phenotype we examined a panel of GC-resistant and sensitive T-ALL cell lines using *in vitro* cell culture assays to provide insights into the modulation of glucose metabolism and association with GC-sensitivity. These studies identified that glucocorticoid resistant leukaemia cells alter their central metabolism and enhance glucose catabolism. We found that GC-resistance is associated with an increased glycolytic phenotype and protection from metabolic crisis in T-ALL. Moreover, we have developed novel metabolomic and proteomic profiling techniques to identify metabolites and

proteins associated with resistance, conducted in collaboration with Metabolomics Australia and Proteomics International. Metabolomic analysis indicated that changes at the metabolic level are associated with drug resistance.

We are currently identifying and delineating significant differentially expressed metabolites and pathways. Together these results indicate that drug-resistant leukaemia cells place unique importance on glucose as a carbon source and this relationship may provide a novel therapeutic opportunity. Understanding the metabolic/ proteomic mechanisms underlying the development of drug resistance in T-ALL is of critical importance for the identification of novel prognostic indicators and the development of more effective antileukaemic drugs.

*This work was supported by the Cancer Council of WA and the Children's Leukaemia and Cancer Research Foundation, WA.*

### TARGETING DRUG RESISTANCE IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

AL SAMUELS, AH BEESLEY, F ONG AND UR KEES IN COLLABORATION WITH B YADAV AND R LOCK, LEUKAEMIA BIOLOGY, CHILDREN'S CANCER INSTITUTE AUSTRALIA FOR MEDICAL RESEARCH, NEW SOUTH WALES.

Drug resistance continues to be a significant problem in childhood T-cell acute lymphoblastic leukaemia (T-ALL), yet few novel therapies have emerged over the last decades. To identify genes and pathways deregulated in drug resistance, as well as small molecule inhibitors that could synergise with current therapies, we have established and validated a T-ALL non-obese

diabetic/severe combined immunodeficient (NOD/SCID) xenograft model of leukaemia relapse. We have developed a novel, clinically relevant four-drug regimen to mimic in mice the initial phase of therapy in paediatric patients. Each xenograft was treated with vehicle control or a combination of vincristine, dexamethasone, L-asparaginase and daunorubicin (VXLD) to derive drug resistant cells *in vivo*. Importantly, the pattern of drug sensitivity in xenografts mirrored the progression of disease in the patients from whom they were derived.

We compared gene transcriptional profiles among the *in vivo* drug-selected T-ALL xenografts and controls to identify genes and pathways associated with drug resistance and ALL relapse (Samuels AL, Beesley AH, Lock RB, Kees UR *et al.* Validation of a Mouse Xenograft Model System for Gene Expression Analysis of Human ALL. *BMC Genomics*, 2010 Apr 21; 11:256). Using this approach we were able to identify potential drug-leads that could synergise with current therapies to reverse the acquired drug resistance. Gene set enrichment and Ingenuity pathways analysis identified key networks, including cellular movement, carbohydrate metabolism and cellular death associated with drug resistance. The Connectivity Map algorithm predicted small molecule inhibitors to reverse the resistant phenotype, including those directed at histone deacetylase, beta-oxidative respiration and hydroxy-methyl-glutaryl Coenzyme A reductase (HMG-CoA). *In vitro* and *in vivo* screenings were conducted to assess the efficacy of several small molecule inhibitors targeting cellular metabolism pathways particularly fatty acid and lipid synthesis. One of the most promising drugs, an HMG-CoA inhibitor

was evaluated *in vivo* as both a single agent and in combination with VXLD. Interestingly, we have found this modulator plus VXLD notably reduced leukaemic infiltration of the bone marrow 2 weeks post treatment initiation, this finding is currently being further evaluated. The results from our study indicated that patients develop distinct yet definable patterns of acquired drug resistance. Therefore to gain a thorough understanding of the mechanisms driving drug resistance and ALL relapse we are generating more xenografts. Primary engraftment for an additional 10 new T-ALL xenografts is underway. We will use transcriptional profiling to examine common and individual patterns among the xenografts to identify genes and pathways contributing to the resistant phenotype. The molecular alterations driving acquired drug resistance will provide important clues for the development of new therapeutic strategies for the treatment of T-ALL.

*This work was supported by the NHMRC, Australia and the Children's Leukaemia and Cancer Research Foundation, WA.*

### INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA AND THE MIXED LINEAGE LEUKAEMIA (MLL) GENE

RS KOTECHA, UR KEES, AH BEESLEY AND NG GOTTARDO IN COLLABORATION WITH CH COLE AND T CARTER, DEPARTMENT OF HAEMATOLOGY-ONCOLOGY, PRINCESS MARGARET HOSPITAL AND A MURCH, KING EDWARD MEMORIAL HOSPITAL FOR WOMEN, PERTH.

In modern medicine, treatment of paediatric acute lymphoblastic leukaemia (ALL) represents one of the many success stories,

with significant improvements in event free and overall survival. However, infant ALL is a heterogeneous group with distinct biological and clinical characteristics, which continues to be resistant to this success. Infant ALL represents 2-5% of paediatric ALL cases. The most common genetic aberration in infant ALL involves the mixed lineage leukaemia (*MLL*) gene, located on chromosome 11q23, which is involved in up to 80% of cases. Most chromosomal rearrangements are associated with leukaemias of a particular lineage. However, 11q23 rearrangements are unique in that they occur in both ALL and acute myeloid leukaemia (AML), hence the term mixed lineage leukaemia. Since discovery of the *MLL* gene in 1992, its recombinome has been the subject of significant scientific research. There have been > 100 translocation partner genes identified, many of which have been characterized at the molecular level. *MLL-EP315/AF1P*, t(1;11)(p32;q23) is a rare fusion, with a paucity of cases reported in the literature. We have recently reported infant monozygotic twins harbouring the t(1;11)(p32;q23) translocation which we are studying to obtain further evidence regarding the pathogenesis of this disease. Molecular analysis and sequencing has confirmed the breakpoint as a novel translocation breakpoint between the *MLL* and *EP315* genes and we are continuing to analyse the features at the genomic level. DNA analysis using Affymetrix 2.7M Cytogenetic Arrays has provided evidence for additional copy-number variations affecting the leukaemias in both twins, challenging the concept that a single genetic defect is sufficient for overt disease in infant *MLL*. The identification of additional genetic abnormalities in such cases may provide opportunities for the development

of novel targeted therapies in this disease.

*This work was supported by the Children's Leukaemia and Cancer Research Foundation, WA, and the Whiteman Fellowship.*

### INTEGRATED TRANSCRIPTIONAL AND EPIGENETIC PROFILING OF DRUG SENSITIVITY IN INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA

MN CRUICKSHANK, J FORD, M HOWLETT, A GOUT, RS KOTECHA, AH BEESLEY AND UR KEES, IN COLLABORATION WITH D ANDERSON AND R FRANCIS, DIVISION OF BIOSTATISTICS AND BIOINFORMATICS.

Current multi-agent treatments have pushed the cure rate for some types of leukaemia to nearly 90%. For infants less than 18 months at the time of diagnosis, the survival rate is only 30%. Intensification of treatment protocols in infants has failed to improve survival but has resulted in large number of toxic deaths. Since treatments using highly toxic chemotherapies are not successful, we have used a high-throughput drug screen to identify novel therapeutic agents. We have generated a panel of eight cell lines derived from five patients with infant acute lymphoblastic leukaemia (iALL) and have subjected them to 101 approved cancer drugs, which is the first comprehensive assessment examining drug responses in iALL. Dose responses clearly showed that some of the currently used drugs are not effectively killing iALL cells, while others were very effective, yet not used in contemporary protocols for infants. Our data demonstrates heterogeneity in drug response among iALL cell lines, however, reproducible drug sensitivity profiles were

observed in independent iALL cell lines derived from the same patient. Despite this variability, we identified nine drugs that were commonly toxic to iALL cells. We found that several of the effective drugs have previously been described as inhibitors of histone deacetylases (HDACs) or DNA methyltransferases (DNMTs). Of the nine drugs, two are HDAC-inhibitors (Romidepsin and Vorinostat), one is a DNMT-inhibitor (Gemcitabine), and three drugs demonstrate DNMT-inhibitory activity *in vitro* (Mitoxantrone, Paclitaxel and Bortezomib). Thus, six of the nine effective drugs identified in our screen, may mediate cytotoxic effects by gene expression changes induced by reprogramming global histone post-translational modifications or DNA methylation.

These reprogramming events, often referred to as epigenetic processes, also mediate embryonic stem cell differentiation and epithelial-mesenchymal transitions; and are therefore essential for development, and often perturbed in cancer. Our data suggest that therapeutic agents targeting epigenetic mechanisms may be useful to treat iALL patients. We are presently examining DNA methylation and gene expression profile alterations that occur in our panel of eight iALL cell lines in response to these drugs. These experiments aim to comprehensively document molecular changes in iALL cells. Identification of such changes that underlie iALL cell drug sensitivity may reveal synergistic pathways that may be exploited, by multi-drug low dose approaches to treat infants.

*This work was supported by the Children's Leukaemia and Cancer Research Foundation, WA.*

## Carcinomas

### MOLECULAR GENETICS OF NUT MIDLINE CARCINOMA

A STIRNWEISS, E FERRARI, AM GOUT, RW FRANCIS, UR KEES AND AH BEESLEY, IN COLLABORATION WITH E BAKER AND A MURCH, KING EDWARD MEMORIAL HOSPITAL FOR WOMEN, PERTH, AND AK CHARLES, PRINCESS MARGARET HOSPITAL, PERTH.

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer that arises in various tissues along the midline of the body (e.g. thymus, thorax or abdomen) and can affect people of any age, including infants. Currently there is no effective therapy for NMC and median survival is less than seven months. The hallmark of the disease is a rearrangement of DNA that joins two genes (called *BRD4* and *NUT*) to create a new hybrid gene that initiates and drives the cancer. Resolving how this *BRD4-NUT* fusion causes cells to grow out of control is a major aim of our research. Importantly, the *BRD4* gene is now implicated in a wide range of cancers and this work thus also contributes to our understanding of other diseases. To study this disease we have a rare panel of NMC cell lines grown from patients diagnosed at the Princess Margaret Hospital. To increase our understanding of the oncogenic mechanism in these NMC cells we undertook next-generation transcriptome sequencing (Illumina RNA-seq) of each line. To look for the expression of gene fusions, we developed an in-house program called *FusionFinder*, designed to detect transcripts containing sequences from two different genes. Analysis of the data from the NMC cell line PER-624 quickly identified a novel transcript in which Exon 15 of *BRD4* was

fused to Exon 2 of *NUT*, therefore differing from all published NMC fusion transcripts. The three additional exons contained in the PER-624 fusion encode a series of polyproline repeats, with one predicted to form a helix. In the NMC cell line PER-403 we identified the 'standard' NMC fusion and two novel isoforms. Knockdown by siRNA in either cell line resulted in decreased proliferation, increased cell size and expression of cytokeratins consistent with epithelial differentiation. These data demonstrate that the novel *BRD4-NUT* fusion in PER-624 encodes a functional protein that is central to the oncogenic mechanism in these cells. Genomic PCR indicated that in both PER-624 and PER-403, the translocation fuses an intron of *BRD4* to a region upstream of the *NUT* coding sequence. Thus the generation of *BRD4-NUT* fusion transcripts through post-translocation RNA-splicing appears to be a common feature of these carcinomas that has not previously been appreciated, with the mechanism facilitating the expression of alternative isoforms of the fusion. Finally, ectopic expression of wildtype *NUT*, a protein normally restricted to the testis, could be demonstrated in PER-403, indicating additional pathways for aberrant cell signaling in NMC. These findings, published in the highly regarded journal *Oncogene*, increase our understanding of the diversity of NMC, and indicate that there are at least two molecular subtypes of the disease. Such knowledge is an important step towards finding therapeutic targets for a disease that is refractory to current treatments.

*This work was supported by the Children's Leukaemia and Cancer Research Foundation, WA.*

## PRE-CLINICAL ASSESSMENT OF THERAPY OPTIONS FOR NUT MIDLINE CARCINOMA

A STIRNWEISS, E FERRARI, UR KEES AND AH BEESLEY.

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer for which there is no effective therapy. Lack of progress in the development of treatment protocols for NMC is attributable both to the voracity of the disease and, until recently, difficulties in its diagnosis. Clinical protocols have essentially been adapted without systematic assessment, and so far with little success. The hallmark of the disease is a chromosomal translocation that disrupts a member of the bromodomain and extra-terminal (BET) protein family known as *BRD4*. Inhibitors that target BET proteins are currently in clinical trial for NMC but data from our laboratory indicate that these drugs are unlikely to be effective in all subtypes of the disease. To identify agents likely to be effective in NMC, we have performed a high-throughput drug screen against NMC cell lines in collaboration with the ACRF Drug Discovery Centre of Childhood Cancer (CCIA, Sydney). This involved comparative testing of the Prestwick Chemical Library of 1200 FDA-approved compounds in NMC vs. non-NMC cell lines. From this we have a shortlist of 15 compounds that we are now testing in a combinatorial fashion to identify those that may act synergistically in NMC cells. These represent a number of distinct drug classes including microtubule inhibitors, anthracyclines, topoisomerase inhibitors, antimetabolites, and anti-inflammatory agents, as well as BET inhibitors and the CDK9 inhibitor flavopiridol. In mice flank-engrafted with NMC cell lines,

we have shown that flavopiridol treatment significantly decreases tumour growth and increases survival without toxicity, establishing the model with which to assess the *in vivo* efficacy of additional agents. Such pre-clinical drug screening is an essential step towards finding effective treatment strategies for an orphaned disease that is refractory to current therapy approaches.

*This work was supported by the Children's Leukaemia and Cancer Research Foundation, and the Telethon Adventurers.*

## Brain tumours

### DEVELOPMENT OF A MOUSE EPENDYMOMA MODEL

R ENDERSBY, H HII AND NG GOTTARDO.

Ependymoma is the third most common brain tumour affecting children and remains incurable in 40% of patients. As is often the case with paediatric brain tumours, survivors are frequently left with devastating long-term neuro-cognitive sequelae. There is an urgent need for more effective and safer therapies. Transgenic mouse tumour models are important tools to facilitate the study of tumour initiation and progression and are invaluable for pre-clinical studies. A genome-wide analysis of human ependymoma specimens demonstrated that all cerebral ependymomas exhibited activated NOTCH signaling and *INK4A/ARF* deletion and that radial glia (RG) were the putative cell of origin of ependymoma. Based on these observations we generated the first mouse model of ependymoma, which phenocopies the human disease precisely by over-expressing

*NOTCH1* in RG cells using the *Btbp* promoter and concurrent deletion of *Ink4a/Arf*. However, the penetrance of ependymoma formation was low (1 to 5%) with a long latency (6 to 18 months), suggesting that additional genetic mutations are required for ependymoma formation, making the current model unsuitable for pre-clinical testing. A more extensive genomic analysis using high resolution SNP genotyping of a larger cohort of human ependymoma specimens (n=230) revealed frequent focal deletions in the tumour suppressor gene *PTEN*. Array comparative genomic hybridisation analysis of mouse ependymomas demonstrated numerous large chromosomal copy number alterations (CAN) as well as focal CAN, common to all tumours, which included the *Pten* locus. Thus, to more faithfully recapitulate the human disease, we are modifying the existing ependymoma mouse model by additionally deleting *Pten*. The development of such a model will be an important tool to enhance our understanding of the biology of this disease and facilitate pre-clinical studies of novel targeted therapies.

*This work was supported by the John Lillie Cancer Research Fellowship (RE and NGG).*

### MOLECULAR GENETICS OF NOVEL PAEDIATRIC BRAIN TUMOUR MODELS

R ENDERSBY

Brain tumours are the leading cause of death among paediatric neoplasms. The commonest malignant brain tumours of infancy and childhood are medulloblastoma (MB), pineoblastoma (PB) and ependymoma (ED). Despite recent therapeutic advances,

the tumours in many patients relapse and are incurable. Moreover, survivors often have significant treatment-related sequelae. To develop more effective therapies, identifying and understanding the genetic events that drive these tumours is critical, as is deducing factors that contribute to therapeutic resistance.

MB, ED and possibly PB, are each comprised of multiple subgroups defined primarily by gene expression profiling. Additionally, a number of recent high-profile publications have further dissected the genetic complexity of MB using whole-genome (WGS) or whole-exome sequencing (WES). These data provide important new insights into the pathogenesis of MB and highlight targets for therapeutic development. However, whilst many targeted anti-cancer agents have recently been developed, evaluation of their efficacy is delayed due to a lack of model systems that accurately reflect the various subtypes of these diseases in children.

To address this, we have generated a panel of unique cell lines representative of various primary and relapsed paediatric brain tumours. Furthermore, to more closely resemble their natural microenvironment, we have established mouse models for these diseases by orthotopic transplant providing a unique resource in the preclinical analysis of novel therapies. However, the preclinical utility of these new models requires full characterization of their underlying genetic alterations such that molecularly targeted therapies are assessed in the most appropriate systems.

Our study aim is to identify mutations across the coding regions of several new models of paediatric brain tumours using whole-exome

capture and deep sequencing. With our models and the results of this study we will be poised to study critical questions about malignant brain tumour biology and be better able to test novel therapies in the most appropriate context.

*This work is supported by the John Lillie Cancer Research Fellowship (RE) and the TICHR small grants scheme.*

## REPURPOSING APPROVED DRUGS TO TREAT CHILDHOOD BRAIN CANCER

TD SCHOEP, RE ENDERSBY, JP MCGLADE, PB DALLAS, NG GOTTARDO.

Brain tumours are the second most common cancer in children and are the major cause of childhood cancer related mortality. This highlights the fact that although survival for children with brain tumours has improved over the last 30 years, survival rates for the past decade have reached a plateau well below that of other childhood cancers, such as leukaemia. Moreover, children that do survive brain tumours suffer debilitating long-term side effects, which significantly impact on their quality of life. After surgery, residual tumour is treated with a combination of intensive chemotherapy and whole brain and spine radiation. However, this approach is devastating to children under three years of age as the radiation kills normal brain cells as well as tumour cells, which has a major impact on subsequent brain development. For this reason, children under three years old are not treated with radiotherapy. However, chemotherapy alone is rarely effective and the tumours in most of these patients grow back. There is therefore a clear need for novel

therapies that increase survival rates. We are identifying drugs that when combined with conventional brain tumour therapies improve the outcomes for the most common childhood brain cancer, medulloblastoma (MB), and the rarer, but highly lethal brain cancer, pineoblastoma (PB). To achieve this, we are performing a high-throughput screen (HTS) using state of the art robotic technology, of thousands of compounds including existing FDA-approved drugs, other pharmaceuticals and known bioactive compounds with the aim of repurposing drugs for the treatment of these cancers. The advantage of repurposing existing drugs is that the pharmacokinetic profiles and toxicities have been extensively characterised, promoting rapid translation into the clinic. The efficacy of compounds will be evaluated alone and in combination with currently used conventional chemotherapeutics in vitro to identify optimal combinations. Their activity will then be validated in vivo using sophisticated animal models of MB and PB established in our laboratory to closely mimic the disease in children. As part of an international drug discovery network, in addition to our HTS approach for drug discovery we are also validating promising therapeutics identified at our drug discovery partner institution, St Jude Children's Research Hospital, in our unique animal models of MB and PB. Our dual approach of repurposing existing, FDA approved drugs for the treatment of childhood brain cancer, and validating new drugs discovered internationally ensures that the best molecules proceed to clinical trial in the shortest amount of time.

*This work is in part supported by the NHMRC, John Lillie Fellowship (NGG), Elliot Parish*

*Research Fellowship and Telethon Adventurers.*

## TESTING NOVEL CHEMOTHERAPEUTICS IN CHILDHOOD BRAIN TUMOUR MODELS

R ENDERSBY, JP MCGLADE, H HII AND NG GOTTARDO.

Whilst many novel targeted anti-cancer agents have been developed, there are few that are used clinically in paediatric brain cancer treatment. One reason is due to the lack of model systems that accurately reflect these diseases in which these novel drugs can be evaluated. Medulloblastoma (MB) and pineoblastoma (PB) are malignant embryonal brain tumors with a propensity to disseminate throughout the central nervous system. Despite significant improvements in therapy, many children remain incurable and survivors are often left with devastating late-effects, highlighting the need for innovative therapeutic strategies that target tumorigenic signaling pathways. To evaluate the efficacy of potential new therapies, as single agents and in combination with conventional chemotherapeutic drugs, we have developed *in vitro* models and orthotopic xenograft systems with a panel of cell lines derived from different MB subtypes and PB. In addition, this study utilizes a transgenic spontaneous mouse model of MB, the *ND2-SmoA1* mouse, which represents the Sonic Hedgehog subgroup of human MBs. We hypothesise that the use of these models will accelerate the evaluation of novel treatment regimens that combine conventional chemotherapeutics with novel targeted agents.

Previous studies have revealed that over-expression of the transmembrane receptors *ErbB2* and *ErbB4* is associated with poor prognosis in children with MB, suggesting that inhibition of this pathway may be of therapeutic benefit. Immunoblot and immunohistochemical analyses have determined that the ErbB pathway is deregulated in several of our *in vitro* and *in vivo* models as observed in children with MB, indicating that these are ideal systems to examine inhibitors of this pathway. We are therefore testing a novel irreversible pan-*ErbB* inhibitor, PF-00299804 (Pfizer Inc.), which has shown anti-tumor activity in lung cancers harboring deregulated ErbB family receptors.

Using our cell lines and standard cellular proliferation assays we have determined the sensitivity of brain tumour cells to conventional anti-cancer therapies currently used in the clinic for these tumours, including vincristine, cyclophosphamide, cisplatin and lomustine (CCNU). We have subsequently investigated how PF-00299804 influences the anti-cancer activity of these drugs and identified synergism when this novel compound is combined with cyclophosphamide or cisplatin. This data has formed the basis for novel combinatorial treatment regimens being tested in a pre-clinical trial using the orthotopic transplant models and the Smo MB model to determine if this is a potential candidate drug to propose for future clinical trials in a subset of patients with this disease.

*This work is supported by the NHMRC, the John Lillie Cancer Research Fellowship (RE and NGG), a grant from Pfizer Inc. and a Princess Margaret Hospital Foundation Translational Research Grant.*

## THE IDENTIFICATION OF DEREGULATED GENES AND PATHWAYS INVOLVED IN THE PATHOGENESIS OF CHILDHOOD EMBRYONAL TUMOURS.

CM BERTRAM, LA GENOVESI, UR KEES, J MCGLADE, H HII, R ENDERSBY, NG GOTTARDO, AND PB DALLAS.

Medulloblastoma (MB) is the most common type of malignant paediatric brain tumour. Although the five-year survival rate for standard risk MB patients is encouraging, the prognosis remains dismal for those with recurrent or metastatic disease. In addition, brain tumour survivors often face serious long-term quality of life issues that can profoundly affect patient and family. The relatively poor outlook for children with brain tumours can be largely explained by the fact that the molecular pathogenesis of MB is only partially understood. The main priority of the brain tumour research program is to address this problem, and ultimately develop safer and more effective drugs and treatment strategies that are urgently required. To achieve this goal we are employing a variety of approaches to investigate the molecular biology of MB.

A subset of MB is thought to arise from the deregulated proliferation of neural stem cells (NSCs) in the developing foetal brain. Hence, the development of MB is likely to be linked to the aberrant activity of signalling pathways that control NSC proliferation, self-renewal and differentiation. As part of our approach to identifying the genes that regulate these pathways, we have analysed the gene expression profiles of our panel of MB cell lines, primary tumour specimens, and human NSCs generated using Affymetrix HG-U133A microarrays. Cross-

comparison of MB expression profiles with normal NSCs and differentiated neural tissues distinguished expression signatures associated with MB pathogenesis from signatures reflecting developmental variation. In addition, the study highlighted a genetic relationship between WNT and SHH-driven MB and CD133+ NSCs, as well as between MB with neuronal differentiation characteristics and foetal germinal matrix cells. Importantly, these data suggest that CD133+ NSCs represent a valuable *in vitro* model system for the study of the pathogenesis of SHH and WNT dependent MB and the development of more efficient subgroup-targeted treatment regimes in the future.

*This work was supported by the NHMRC, Australia and the Children's Leukaemia and Cancer Research Foundation, WA.*

## THE CHARACTERISATION OF DEREGULATED MICRORNA EXPRESSION IN MEDULLOBLASTOMA

LA GENOVESI, JL BEARFOOT, K CARTER, NG GOTTARDO, AND PB DALLAS IN COLLABORATION WITH KM GILES OF THE WESTERN AUSTRALIAN INSTITUTE FOR MEDICAL RESEARCH, PERTH.

MicroRNAs (miRNAs) are a large class of short non-coding RNAs that regulate growth and development in eukaryotic cells. It is now clear that deregulated miRNA expression plays an important role in the pathogenesis of many different types of cancer, including adult brain tumours. Recent data suggest that deregulated miRNA expression may also play a significant role in the pathogenesis of MB. To address this issue in more detail we analysed the

expression levels of a panel of 754 miRNAs in MB specimens and neural stem cells (NSCs) using qRT-PCR in a low-density array format. We identified 33 differentially regulated miRNAs in primary specimens relative to CD133+ NSCs. Interestingly, several of the over-expressed miRNAs were predicted to target *FOXO1A* raising the possibility that down-regulation of *FOXO1A* expression in MB may be linked to deregulated miRNA expression. Several deregulated miRNAs mapped to chromosome 14q32, and integrative analyses with inversely correlated predicted target genes revealed enrichment of pathways related to neuronal migration, nervous system development and cell proliferation. We also identified a link between deregulated expression of members of the mir-200 miRNA family, which are important regulators of epithelial-mesenchymal transition, in specific MB subtypes. We anticipate that ongoing research based on these data will rationalise our understanding of the fundamental molecular mechanisms that initiate and maintain the brain tumour phenotype.

*This work was supported by the Raine Medical Research Foundation and Cancer Council of Western Australia.*

## NOVEL PEPTIDE BASED DRUGS FOR THE TREATMENT OF SONIC HEDGEHOG DEPENDENT MEDULLOBLASTOMA

PB DALLAS, J VARANO, TD SCHOEP, R ENDERSBY, NG GOTTARDO, IN COLLABORATION WITH N MILECH, B LONGVILLE, R HOPKINS, DRUG DISCOVERY GROUP, TICHR

Medulloblastoma (MB) is the most common

malignant brain tumour in children, and a leading cause of paediatric cancer related mortality and morbidity. Recently, drugs that target Smoothed (SMO), which is a component of the sonic hedgehog (SHH) pathway, have shown great promise for the treatment of MB. However, there are drawbacks with these new SMO targeting drugs, particularly associated with the development of resistance. Phylomers are a unique type of peptide-based drug developed by the drug discovery company Phylogica, which may be particularly suitable for avoiding the drug resistance problem, and may open new avenues for effective MB therapeutics that have yet to be exploited. In addition, Phylomers that are effective for the treatment of MB may also be effective for other types of cancer, including basal cell carcinomas, the majority of which are associated with altered SHH pathway activity. Preliminary data suggest that several Phylomers we have identified are capable of blocking SHH pathway activity *in vitro*. If the inhibitory activity of these Phylomers can be recapitulated *in vivo*, Phylomers may ultimately provide a new treatment option for MB patients.

*This research is supported by the Telethon Adventurers.*

## Staff and Students

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### RESEARCH SUPPORT

Stewart Cattach

## Awards

Meegan Howlett, Children's Leukaemia and Cancer Research Foundation Travel Grant

Peter Dallas, Nicholas Gottardo, Kim Carter, Keith Giles, Cancer Council of Western Australia Project Grant.

Nicholas Gottardo and Peter Dallas, PMH Foundation Translational Research Grant.

Nicholas Gottardo, Peter Dallas, in collaboration with D Ashley, TG Johns, Pfizer Investigator initiated grant.

Raelene Endersby. Telethon Institute, Child Health Research Seminar Series – Presenter of the year award.

Nick Gottardo, Ursula Kees, Raelene Endersby NHMRC Project Grant.

Raelene Endersby, Telethon Institute for Child Health Research, Small Grant (2012, 1 year).

## External Committees

### INTERNATIONAL

Ursula Kees, Chair COG-B969 Study Committee (Children's Oncology Group), Arcadia, CA USA.

Nicholas Gottardo, Children's Oncology Group.

Central Nervous System Tumour Committee

### NATIONAL

Amy Samuels, Australian Society for Medical Research (ASMR), 2008-present.

Peter Dallas. Australasian Society for Stem Cell Research conference organising committee.

Nicholas Gottardo. Medical Advisory Committee. The Cure Starts Now Foundation.

Nicholas Gottardo. Australian Children's Cancer Trials (ACCT) Principal Investigator.

Nicholas Gottardo. Australian Children's Clinical Trials (ACCT) group. Board member and Principal Investigator for Western Australia.

Raelene Endersby. Australian Early-Mid Career Researchers Forum, Australian Academy of Science.

### LOCAL

Ursula Kees, The Cancer Council of Western Australia, Research and Scientific Advisory Committee.

## Invited Presentations

Ursula Kees, Australian Prosthodontic Society Inc (WA Branch) AGM, Perth, June 2012. CLCRF studies into cancer and leukaemia in children.

Ursula Kees, 4th New Directions In Leukaemia Research, Brisbane, March 2012. Independent clonal evolution and cellular heterogeneity in monozygotic infant twins with acute leukaemia carrying a novel *MLL-EP315* translocation.



Alex Beesley, Next Generation Cancer Research: Where are we now, and where are we heading? *Australian Society for Biochemistry and Molecular Biology (ASBMB) Annual Symposium, Fremantle, WA. 2012*

Alex Beesley (Invited Speaker 2012). Nut Midline Carcinoma: Targeting a disease without cure. *Children's Cancer Institute Australia (CCIA), Visiting Seminar Program, Sydney 2012.*

Alex Beesley, New Directions and Opportunities in Cancer Research. *Rotary-Lions Club South West Bike Trek Fundraiser, Bunbury, WA. 2012*

Amy Samuels, Targeting metabolism to overcome glucocorticoid resistance in paediatric acute lymphoblastic leukaemia, Perth Cancer Club, Perth, November 2012.

Meegan Howlett, Connective Tissue Growth Factor (CTGF) Mediates Cell-Cell Interactions In The Leukaemic Bone Marrow Microenvironment. 4th New Directions in Leukaemia Research, QLD, AUS.

Raelene Endersby. Akt Inhibition Prolongs Survival and Decreases Proliferation in a Mouse Model of High-grade Glioma. 26th Lorne Cancer Conference. Lorne, Victoria. Feb 2012.

Raelene Endersby. Paediatric brain tumours: Mouse modeling to preclinical studies. Centre for Cancer Biology. Adelaide, Australia, Aug 2012.

Raelene Endersby. Paediatric brain tumours: Mouse modeling to preclinical studies. Flinders Centre for Innovation in Cancer. Adelaide, Australia, Aug 2012.

## ACTIVE collaborations

Prof M Norris & Prof M Haber. Experimental Therapeutics Program, Children's Cancer Institute Australia for Medical Research

Prof R Lock, Leukaemia Biology Program, Children's Cancer Institute Australia for Medical Research

Dr Richard Lipscombe, Proteomics International, Perth, Australia.

Metabolomics Australia, University of Western Australia, Perth, Australia

Prof C Mullighan St Jude Children's Research Hospital, Memphis TN, USA

Prof W Alexander and Dr R Dickins, Walter and Eliza Hall Institute of Medical Research, Melbourne

Prof D Brigstock, Children's Research Institute, Columbus OH, USA

Dr M Garnett, Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, UK

Dr G. Arndt, ACRF Drug Discovery Centre for Childhood Cancer, Children's Cancer Institute Australia for Medical Research, Sydney

Prof C. Cole, Dr M Phillips and Dr A Charles, Department of Paediatric and Adolescent Haematology and Oncology, Princess Margaret Hospital for Children

Novartis Pharma AG, Basel, Switzerland, NMC Carcinoma Project

GlaxoSmithKline R&D, Brentford, UK, NMC Carcinoma Project

Dr Christopher French, Women and Brigham's

Hospital, Boston

Dr A Murch, Cytogenetics Department, King Edwards Memorial Hospital, Perth

Dr Bernard Callus, School of Chemistry and Biochemistry, University of Western Australia, Perth

Prof Peter Leedman and Dr Keith Giles, Western Australian Institute of Medical Research, Perth

Prof Terry Johns, Monash Institute for Medical Research, Melbourne.

Pfizer Inc, New York, USA

# DIABETES AND OBESITY

## Overview

The Diabetes and Obesity Research team aims to improve the lives of children and adolescents affected by Type 1 and Type 2 Diabetes and obesity by researching these conditions. Our research addresses relevant clinical questions and encompasses epidemiology, clinical investigations, clinical trials, new technology in disease management and prevention studies.

The team conducts research in collaboration with the Department of Endocrinology and Diabetes in Princess Margaret Hospital for Children, Perth; the School of Sports Science and Exercise Health, Psychology, University of Western Australia; the Western Australian Institute for Medical Research, and collaborators from diabetes research centres interstate and overseas.

The group commenced several major new projects in 2012, including investigating the use of a predictive low glucose suspend function in insulin pumps for Type 1 diabetes; researching the environmental determinants of Type 1 Diabetes in collaboration with interstate diabetes research centres; and researching Disease Subtypes and Phenotypes of Type 1 and Type 2 diabetes.

## Type 1 Diabetes

CLINICAL PROF TIM JONES; ASSOC CLINICAL PROF LIZ DAVIS

## Type 1 Diabetes Epidemiology

EPIDEMIOLOGY OF CHILDHOOD-ONSET TYPE 1 DIABETES IN WESTERN

## AUSTRALIA

LIZ DAVIS, AVENI HAYNES, MATT COOPER, CAROL BOWER

The objectives of this study are:

- To study the epidemiology of childhood onset diabetes in children aged 0-16 years in Western Australia from 1985 onwards.
- To test for differences in incidence rates by year of diagnosis, age of diagnosis, sex, month of diagnosis, birth month and place of residence at diagnosis.
- To identify potential antenatal and perinatal antecedents to childhood-onset diabetes e.g. birth weight, gestational age, birth order and maternal age.

These aims will be achieved by means of data linkage using the Western Australian Children's Diabetes Database, and Western Australian Midwives' Notification System. The study population will be all children diagnosed with childhood-onset diabetes before the age of 15 years, who were resident in Western Australia at the time of diagnosis. The study period will be from January 1985 to December 2010. There are over 1500 cases in the diabetes register at Princess Margaret Hospital that meet these inclusion criteria. Cases in the Western Australian Children's Diabetes Database at Princess Margaret Hospital will be linked to records in the Western Australian Midwives' Notification System using the unique personal identification number assigned to individuals in the Western Australian Health Department databases.

*Funding Source: Department of Endocrinology & Diabetes, PMH*

## EPIDEMIOLOGY OF HYPOGLYCAEMIA IN CHILDHOOD-ONSET DIABETES IN WESTERN AUSTRALIA

TIM JONES, LIZ DAVIS, MATT COOPER

Hypoglycemia and the subsequent effects of hypoglycemia remain the primary fear for children and their parents in adequately managing the treatment of Type 1 Diabetes (T1D). It is reported that over the past decade the overall incidence of severe hypoglycemic events has declined relative to the previous decade. In this study we investigate the demographic, lifestyle and diabetes management factors associated with the incidence of severe hypoglycemia to provide clinicians and diabetes educators with knowledge on which patients may be at higher risk of severe hypoglycemia.

The aims of this study are:

Report the incidence of severe hypoglycemia over the past decade in the WA childhood T1D onset cohort

Calculate the relative risk for the association of demographic, lifestyle and management factors (including but not limited to age, length of diagnosis, BMI, insulin regime) with the incidence of severe hypoglycemia.

*Funding Source: Internal Funds*

## INVESTIGATING MORTALITY RATES AND THE INCIDENCE AND RISK FACTORS OF DIABETES COMPLICATIONS AND CO-MORBIDITIES DURING EARLY ADULT LIFE IN A POPULATION BASED CHILDHOOD ONSET DIABETES

## COHORT

LIZ DAVIS, MATT COOPER, AVENI HAYNES, TIM JONES

The education and treatment regimes for children with Type 1 Diabetes (T1D) are constantly evolving, and the introduction of and improvements to new technologies adds to the complexity of the management of T1D. Studies have been done in the past to provide insight into the complications and co-morbidities in adulthood for this with childhood onset Type 1 diabetes, but little is known about how the changes to diabetes management affect the incidence of these complications and co-morbidities, as this is something that can only be revealed with time. This project will use the Western Australian Data Linkage System (WADLS) to provide novel information of the incidence and relative risk of T1D co-morbidities and mortality during early adulthood in a modern clinical setting. The primary source of the study population is the Western Australian Children's Diabetes Database. The WADLS contains data uploaded from the Hospital Morbidity Data Collection; the Emergency Department Data Collection; the Mental Health Information System; the Birth, Death and Marriages Registry and the Western Australia Electoral Commission records. The WADLS will enable the selection of matched controls from the birth registry. All subjects in WA diagnosed with T1D prior to age 16 who were 18 years or older at 30th June 2010 (n=1,376) are considered eligible for entry into this analysis.

The aims of this study are:

- To identify the incidence of diabetes complications and co-morbidities seen in early adulthood (<40 years) in a childhood

onset T1D population-based cohort.

- To calculate the risk (relative to age and sex matched controls) for incidence of diabetes complications and co-morbidities in early adulthood (<40 years) associated with childhood onset T1D in a population-based cohort.
- To compare the all-cause mortality rate, and cause of death in early adulthood (<40 years) in a childhood onset T1D population-based cohort to general population age and sex matched controls.
- To examine the impact of risk factors observed during childhood on the incidence of diabetes complications, co-morbidities and cause of death in early adulthood (<40 years) in a childhood onset T1D population-based cohort.

*Funding Source: Diabetes Research Fund*

## TRIALNET: PATHWAY TO PREVENTION

LOCAL INVESTIGATORS: TIM JONES, LIZ DAVIS

STUDY STAFF: JULIE DART, HEATHER ROBY;  
NIRUBASINI PARAMALINGAM; ADAM  
RETTERTH

The overall objective of this multi-centre international study is to perform baseline and repeat assessments over time of the metabolic and immunologic status of individuals at risk for Type 1 diabetes (T1D). This is in order to:(a) characterize their risk for developing T1D and identify subjects eligible for prevention trials, (b) describe the pathogenic evolution of T1D, and (c) increase the understanding of the pathogenic factors involved in the development of T1D.

The specific objectives of this study are:

1. To determine the risk for the occurrence of T1D according to glucose tolerance tests, C-peptide levels, islet autoantibodies, HbA1c levels, markers of cell-mediated immunity, and genetic markers associated with T1D.
2. To examine the accuracy of TrialNet measures in predicting future T1D.
3. To characterize the progression of immunologic abnormalities in the development of T1D by serially studying islet autoantibodies and immune mechanistic studies.
4. To characterize the progression of metabolic decompensation in the development of T1D by serially studying insulin, C-peptide, other islet hormones, HbA1c and glucose levels, and to identify immunologic and other factors associated with this decompensation.
5. To determine the incidence of severe acute metabolic decompensation as the initial clinical presentation in individuals who have been identified as being at increased risk for T1D.
6. To identify individuals who qualify for TrialNet T1D prevention trials.
7. To accrue additional information about immunologic and metabolic factors related to the pathogenesis of T1D and validate new methods or tests that mark disease progression or response to therapy.
8. To accrue additional information about genomic markers associated with risk for

the development of T1D.

9. For those participants who participated in the DPT-1 study, to examine associations of characteristics (e.g. demographics, immunologic, metabolic, etc.) assessed during the DPT-1 study with characteristics and outcomes assessed in TrialNet.

The primary outcome of this prospective cohort study is the development of diabetes as defined by the American Diabetes Association (ADA) based on glucose testing, or the presence of symptoms and unequivocal hyperglycaemia.

Participant eligibility: (1) Having a first degree relative (parent, sibling, child) with T1D, and aged 1 – 45 years; (2) having a second and third degree relative (nieces, nephews, aunts, uncles, grandparent, cousins, half-siblings) with T1D and aged 1 – 20 years.

*Funding Source: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the National Centre for Research Resources (NCRR), the Juvenile Diabetes Research Foundation International (JDRF), and the American Diabetes Association (ADA)*

## EARLY ENVIRONMENTAL DETERMINANTS OF PANCREATIC ISLET AUTOIMMUNITY: A PREGNANCY TO EARLY LIFE COHORT STUDY IN CHILDREN AT RISK OF TYPE 1 DIABETES (T1D)

LOCAL INVESTIGATORS: TIM JONES, LIZ DAVIS

STUDY STAFF: WAYNE SOON

This is a multi-centre study involving researchers in South Australia, Victoria, New South Wales, Western Australia and Queensland. The study is coordinated by Prof Jenny Couper in South Australia.

This prospective cohort follows children who are at risk of developing T1D from the gestational period into the first 3 years of life. Pregnant women who have Type 1 diabetes or where their unborn child has a first degree relative with T1D are recruited to the study. The infants are monitored for genotype, weight gain, insulin sensitivity, changes in the metabolome and microbiome, vitamin D and omega 3 fatty acid status, and the timing and frequency of viral infections. This is in order to determine the relationship between weight gain, insulin sensitivity, nutritional status and viral infection, and the development of persistent islet autoimmunity in these children.

The primary outcome measure is islet autoimmunity defined as persistent elevation of > 1 islet autoantibodies on consecutive 6 monthly tests, including the most recent. This will exclude transient, low titre autoantibodies.

*Funding Source: NHMRC 1025082*

## IDENTIFYING MOLECULAR SIGNATURES OF TYPE 1 DIABETES

INVESTIGATORS: PROF GRANT MORAHAN, TIM JONES, LIZ DAVIS

STUDY STAFF: HEATHER ROBY

We aim to identify genes and genetic pathways associated with the autoimmune destruction of beta cells, and characterise the transcriptomic

and proteomic changes of the T1D process. This will potentially:

- increase our understanding of the pathophysiology of T1D;
- allow us to more finely stratify people most at risk of developing T1D;
- discover biomarkers of the activity of the T1D process, which may allow clinical intervention in the “honeymoon period” before all beta cell mass is lost.

100 patients presenting to PMH with onset of T1D will be recruited to the study. Blood samples will be collected at diagnosis and at the 3-18 month follow-up clinic.

This study aims to measure changes in molecular systems at the time of onset of childhood T1D, and relate these changes to the patients’ genotype for known T1D risk genes. The systems of interest are gene expression (transcriptome) in circulating WBCs and plasma protein composition (the plasma proteome) circulating WBC IFN $\gamma$  production.

The approach of correlating gene expression and underlying genetic variation has recently been termed “systems genetics”. The approach has been pioneered in rodent models, but has not been applied to proteomics, diabetes research or to research in humans.

The strength of this approach lies in the lack of assumptions that are taken into the data gathering process. Hypotheses are generated after data gathering and analysis. These hypotheses can then be validated using alternate “hypothesis-testing” experimental designs.

*Funding Source: NHMRC 305500; Diabetes*

*Research Foundation of WA*

## Type 1 Diabetes Management

### HOW DO HIGH PROTEIN AND/OR HIGH FAT MEALS AFFECT POSTPRANDIAL GLYCAEMIC CONTROL IN CHILDREN USING INTENSIVE INSULIN THERAPY?

LOCAL INVESTIGATORS: LIZ DAVIS; MEGAN EVANS

This dual-site study is investigating the effect of fat and protein content of a standardized carbohydrate meal, on the post-prandial glycaemic response in children with type 1 diabetes who are on multiple daily injections or insulin pump therapy. The study design is a randomised 4 armed cross-over trial, where the glycaemic fluctuations in the 180min following the meal is traced using a continuous sub-cutaneous glucose monitoring system.

58 children between the two participating sites having the following inclusion criteria will be recruited: aged- 7-18 years inclusive; on 4 or more insulin injections per day, or on insulin pump therapy; diagnosed with type 1 diabetes, at least over 6 months ago; with HbA1c  $\leq$  8.0% at last clinic visit. Exclusion criteria are: Coeliac disease; Hyperlipidaemia; history of poor compliance or attendance; Unable to commit to full study protocol.

*Funding Source: Pfizer APEC Research Grant*

### LOW GLUCOSE SUSPEND STUDY

INVESTIGATORS: TIM JONES, TRANG LY  
STUDY STAFF: JENNIFER NICHOLAS, ADAM

RETTERRATH

A new pump has just been released, the Paradigm Veo pump. This pump has the new feature of detecting low glucose levels (hypoglycaemia) and automatically switching off insulin infusion for 2 hours if the blood glucose level is low. This will be helpful in reducing the severity of an episode of hypoglycaemia.

The aim of this study is to see if using the Paradigm Veo pump for a period of 6months can reduce the rate of severe hypoglycaemia, particularly for patients who have lost some of the symptoms that would normally alert them to a low blood glucose level. In a subgroup of 16 adolescents, we will also look at their hormone and symptom responses during hypoglycaemia.

Patients aged between 4 years and 50 years with T1D on insulin pump therapy with impaired awareness of hypoglycaemia will be eligible to participate.

Patients will be randomised to either the Paradigm Veo (low glucose suspend feature and continuous glucose monitoring) or continue on their standard pump (no low glucose suspend capability and no continuous glucose monitoring).

*Funding Source: Juvenile Diabetes Research Foundation*

### EFFECT OF EXERCISE INTENSITY ON THE RATE OF GLUCOSE ADMINISTRATION REQUIRED TO MAINTAIN STABLE GLYCAEMIA WHEN PLASMA INSULIN IS AT BASAL LEVELS IN INDIVIDUALS WITH TYPE 1 DIABETES MELLITUS

INVESTIGATORS: VINUTHA SHETTY, PAUL FOURNIER, TIM JONES, LIZ DAVIS

STUDY STAFF: RAY DAVEY, NIRUBASINI PARAMALINGAM, ADAM RETTERATH, HEATHER ROBY

Regular exercise provides a number of well documented health benefits for individuals with type 1 diabetes. Unfortunately for insulin treated type 1 diabetes individuals, particularly those in good glycaemic control, exercise increases the risk of severe hypoglycaemia. This increased risk of hypoglycaemia occurs not only with exercising, but also for several hours during recovery. One approach to reduce the risk of hypoglycaemia associated with exercise is to reduce insulin dose before exercise. Another is to consume extra carbohydrates during and/ after exercise, but the current guidelines for treatment of hypoglycaemia do not provide practical information about the amount of CHO necessary to prevent hypoglycaemia during exercise.

This proposed study aims to determine more precisely the amount of glucose intake that is required to prevent hypoglycaemia during exercise; under basal insulin conditions. In addition, we will investigate how glucose requirements is affected by exercise intensity and how this relationship responds to confounding factors such as prevailing insulin and glucose levels. This study will involve one group ten healthy, active type 1 diabetic individuals (male and female) aged between 13 and 25 years old. All participants will undergo four testing sessions involving cycling on a stationary bike at four different workloads – 35%, 50%, 65% and 80% VO<sub>2</sub> Peak.

Primary outcome: Precise estimate of the

glucose requirements to maintain stable glucose levels over a range of exercise intensities under basal insulin condition.

Secondary outcome: Determining the extent to which changes in glucose requirements result from changes in glucose production and utilisation rates.

*Funding Source: Pfizer APEC Research Grant; PMH Foundation Grant*

## Type 1 Diabetes Technological Advances

### PREDICTIVE LOW GLUCOSE SUSPEND STUDY – STAGE 1

LOCAL INVESTIGATORS: MARY ABRAHAM; MARTIN DE BOCK; LIZ DAVIS; TIM JONES  
STUDY STAFF: RAY DAVEY; JULIE DART; HEATHER ROBY; ADAM RETTERATH; NIRUBASINI PARAMALINGAM; CASEY LOWDEN-CROOK

The availability of continuous glucose monitoring systems is an important advancement in the pursuit of a fully automated closed-loop system. An initial stage in the development of such a system has been the availability of a system that automatically suspends basal insulin delivery for a pre-determined period if patients do not respond to alarms. Whilst this is a major step forward, the capacity to suspend insulin delivery when impending hypoglycaemia is predicted offers the additional advantage of reducing the actual time spent hypoglycaemic. If effective and safe this system is likely to reduce the burden of diabetes care as well as allow more intensive attempts to improve glycaemic control.

This study will aim to test a novel algorithm

for hypoglycemia prediction, under conditions of excess insulin and moderate intensity exercise, to determine if the response of insulin suspension to these different conditions which predispose hypoglycaemia differs. Crucial to the effectiveness of a preventive system and the prevention of post suspend hyperglycemia will be a complimentary algorithm that activates the resumption of insulin delivery. By studying post suspend glucose values under controlled conditions we will generate such data. In addition, although previous studies have utilized increased basal insulin delivery as a method of inducing hypoglycaemia, in our study we will utilize increased bolus insulin delivery-the scenario more likely to be encountered in a real-life setting.

Study participants will be: adolescents and young adults age from 12 to 26 years with type 1 diabetes; duration of diabetes > 1 year and on treatment with an insulin pump; HbA1c < 8.5%

The aims of this study are: (1) To determine the blood glucose profile with a predictive low glucose suspend (PLGS) algorithm versus no insulin suspension (control) following hypoglycemia induced by a bolus of subcutaneous insulin; (2) To determine the blood glucose profile with a PLGS algorithm versus no insulin suspension (control) following hypoglycemia induced by moderate intensity exercise; (3) To analyse the pattern of blood glucose and ketone levels following pump suspension in both scenarios, and use these to assist with determination of parameters for insulin pump resumption.

*Funding Source: JDRF*

## Type 1 Diabetes Complications

### ADOLESCENT TYPE 1 DIABETES CARDIO-RENAL INTERVENTION TRIAL

LOCAL INVESTIGATORS: TIM JONES; LIZ DAVIS  
STUDY STAFF: ALISON ROBERTS; MARY ABRAHAM; MARTIN DE BOCK; CARLY GEORGE; VINUTHA SHETTY; JULIE DART; ADAM RETTERATH; JENNIFER NICHOLAS; HEATHER ROBY; BARBARA SHEIL

This is an international clinical trial with the primary objectives of determining whether intervention with Angiotensin Converting Enzyme Inhibitors (ACEI), Statins, or a combination of both, when compared with placebo, will: (1) reduce albumin excretion as assessed by six monthly measurement of albumin/creatinine ratio (ACR) in 3 early morning urines; (2) reduce the incidence of microalbuminuria (MA) (ACR log mean > 3.5 mg/mmol (males) or > 4 mg/mmol (females) in 2 out of 3 urines) at the end of the study period; (3) reduce the incidence of MA during the six month run out period following the completion of intervention phase.

This study will aim to recruit 500 adolescents with the following criteria: adolescents aged 11-16 years; with type 1 diabetes of >1 year duration; identified as being at high risk for the development of DN and CVD as predicted by albumin excretion in the upper tertile after appropriate adjustment for age, sex, age at diagnosis and duration of disease. Recruitment closes in June 2012. It is a four-armed randomised clinical trial involving: (1) Quinapril: starting dose 5mg increased to 10mg daily after 2 weeks, (2) Atorvastatin, 10mg daily, (3) Quinapril + Atorvastatin, (4) Placebo.

*Funding Source: JDRF; BHF*

### AUSSI-ADDIT

LOCAL INVESTIGATORS: TIM JONES; LIZ DAVIS  
STUDY STAFF: JULIE DART; ADAM RETTERATH ; ALISON ROBERTS

This multi-centre study is investigating the changes in retinopathy, aortic intima media thickness (aIMT) and heart rate variability which are indicators of macrovascular disease and autonomic neuropathy respectively; which are complications of Type 1 diabetes.

The study's aims are: (1) To determine whether adolescents with T1DM found to be at high risk of microalbuminuria have evidence of accelerated atherosclerosis, retinopathy and autonomic neuropathy as compared to adolescents at lower risk of microalbuminuria. (2) To determine whether ACE inhibition and or statin therapy during puberty will slow the progression of microvascular and macrovascular disease in T1DM

The study population is adolescents aged 11.0y to 16.9y, and with type 1 diabetes mellitus; screened as being at low risk or high risk for developing diabetic nephropathy and cardiovascular disease. Throughout Australia 370 adolescents deemed at high and 200 adolescents deemed at low in the Microalbuminuria Screening Study. The study duration is 6 years, and includes a two year recruitment period and a 4 year follow-up period. The study endpoints are changes in retinal images, aIMT and heart rate variability measures, after 4 years duration from baseline.

*Funding Source: NHMRC Grant #632521*

## NEUROCOGNITIVE OUTCOMES OF CHILDREN WITH TYPE 1 DIABETES MELLITUS

INVESTIGATORS: TIM JONES; MIKE ANDERSON; LIZ DAVIS

STUDY STAFF: KAITIE MCNAMARA; SHOSHANA RATH

Previous research has indicated that children with type 1 diabetes mellitus (T1DM) may experience deficits in their neurocognitive development compared with healthy children. Whilst the impact that T1DM has on the developing brain remains controversial, evidence suggests that these deficits may reflect the occurrence of episodes of severe hypoglycaemia. Previous studies have found a link between hypoglycaemia history and cognitive ability on a number of cognitive domains including verbal IQ, verbal memory short-term memory and attention. These findings are not always replicated and, as yet, there is no consensus as to how episodes of severe hypoglycaemia affect the developing brain. Our previous study however indicated that performance on tasks of executive function and fluid intelligence was significantly poorer in individuals with T1DM, and there is a suggestion of associated differences in frontal functioning as indicated by ERP (event-related potential) studies.

The main aim of the Neurocognitive Outcomes study is to conduct an analysis of children with T1DM's cognitive profile at an age in which both cognition and cortical development are still maturing (7-11 years). This will be achieved through the use of neurocognitive assessment, electroencephalogram (EEG) technology and magnetic resonance imaging (MRI) screens. We are also analysing the cognitive profile of a

healthy sibling comparison group. In particular we will test the hypothesis that if there are cognitive deficits associated with T1DM, they are more likely to be found in measures of fluid intelligence and executive (frontal) functions. This study is run in collaboration with the Neurocognitive Development Unit at the School of Psychology, UWA.

*Funding Source: PMH Foundation; APEG grant*

## Type 1 Diabetes Prevention

### INTRANASAL INSULIN TRIAL II

LOCAL INVESTIGATORS: LIZ DAVIS; TIM JONES

STUDY STAFF: ALISON ROBERTS; VINUTHA SHETTY; NIRUBASINI PARAMALINGAM; JACQUELINE CURRAN; ADAM RETTERATH

The Type 1 Diabetes Prevention Trial, also known as the Intranasal Insulin Trial (INIT II), is part of a coordinated global effort to develop a vaccine for type 1 diabetes. The trial, which began in 2006, is jointly funded by the National Health and Medical Research Council (NHMRC) and the Juvenile Diabetes Research Foundation, through the Diabetes Vaccine Development Centre.

If successful, this vaccine could prevent type 1 diabetes and the need for daily insulin injections in people at risk. Over the past 5 years, over 6,500 people have been screened in Australia. Before someone is diagnosed with diabetes, there is a period of time, often many years, when there are no symptoms, but the body's immune system has already begun attacking the insulin-producing cells in the pancreas. This time provides a potential opportunity to prevent further destruction of the beta cells and thus the onset of type 1 diabetes.

INITII is recruiting relatives of people with type 1 diabetes. Relatives have an increased risk of developing diabetes, which can be assessed by a simple blood test. Only 2% of the people tested will be considered at high risk of developing diabetes and be eligible to enter this trial. Testing for this study is free and can be done either at PMH or at the local blood collection centre.

*Funding Source: NHMRC; JDRF*

### ORAL INSULIN TRIAL

LOCAL INVESTIGATORS: TIM JONES; LIZ DAVIS

STUDY STAFF: JULIE DART; HEATHER ROBY; NIRUBASINI PARAMALINGAM; ADAM RETTERATH

The TrialNet Oral Insulin Diabetes Prevention Study is being conducted internationally, to see if giving insulin by mouth (in a capsule) will delay or prevent T1DM in people at increased risk of developing diabetes.

Participants attend the hospital for an initial, a baseline (Randomization), a 3-month follow-up visit and then follow-up visits 6-monthly for the rest of the study. At each study visit, participants are asked questions about their health, activity, diet and about diabetes in their family and will also have a physical examination and blood tests. At the Baseline Visit, participants are randomly assigned to receive either active treatment with insulin capsule (7.5 mg insulin) or an inactive dummy capsule called placebo.

*Funding Source: NIDDK; NIAID; NICHD; NCRR; JDRF; ADA*

## Type 2 Diabetes

ASSOC CLINICAL PROF LIZ DAVIS

## Type 2 Diabetes Epidemiology

### EPIDEMIOLOGY OF T2DM IN CHILDHOOD AND ASSOCIATED DISEASE COMPLICATIONS

LIZ DAVIS; RACHELLE KALIC

This study is investigating the incidence of childhood Type 2 Diabetes in the Western Australian community, and the incidence of diabetes-related complications and related cardiovascular risk factors such as hypertension and hyperlipidaemia in that population

*Funding Source: Internal*

## Type 2 Diabetes Management

### CAN EXERCISE TRAINING IMPROVE HEALTH IN YOUNG PEOPLE WITH TYPE 2 DIABETES?

INVESTIGATORS: LIZ DAVIS; DANNY GREEN; LOUISE NAYLOR

STUDY STAFF: NORHAIDA MOHD YUSUF; NIRUBASINI PARAMALINGAM; MARY ABRAHAM; RACHELLE KALIC

Over the last few years, T2DM and obesity is becoming more common in young people. Individuals with T2DM and obesity often have high blood glucose, the effects of which can cause other major health problems such as heart or kidney disease. However studies have shown that we may be able to avoid the effects of constant high blood glucose by improving blood glucose control within the first few years of

diagnosis. One way of improving blood glucose control is through exercise.

We are studying how exercise in young people with T2DM, and obese young people at risk of developing type 2 diabetes, affects: (1) The function of small and large blood vessel, and whether an exercise training program can improve function, (2) How well the body uses insulin, and (3) Whether exercise training can improve blood glucose control.

*Funding Source: Pfizer APEC grant # WS1836718*

## Obesity

LIZ DAVIS

The 2007-2008 Australian National Health Survey found that 25.1% of children aged 5-17 years in Western Australia are overweight or obese (ABS, 2011). The Obesity Research Team at Telethon Institute for Child Health Research together with the Department of Endocrinology and Diabetes at the Princess Margaret Hospital for Children, are researching the causes of obesity and interventions to combat obesity.

Investigators are collecting DNA and serum to investigate the genetic factors and biomarkers that are potential risk factors for weight gain in children and adolescents, the development of obesity-related complications, and protective factors against these complications. By collecting information on the development of obesity and successful interventions, investigators hope to alleviate the burden of childhood obesity

The team is also investigating physical, psychological and dietary factors contributing to sustainable weight loss and improved health

in children and adolescents participating in the Department's lifestyle intervention programs, and participants in the trial of a new weight loss device.

## Obesity Intervention

### BIOENTERIC INTRAGASTRIC BALLOON IN OBESE ADOLESCENTS

INVESTIGATORS: JACQUELINE CURRAN; LIZ DAVIS; COLIN SHERRINGTON; TIM JONES  
STUDY STAFF: RACHELLE KALIC; LUISE RUSSELL; DEANNA MESSINA; ANNA TREMAYNE

Weight loss treatments for adolescents who are overweight or obese include lifestyle changes that include diet, exercise, parental involvement, reinforcement, stimulus control and self-monitoring as targeted interventions. These lifestyle interventions in children have found to result in a mean sustainable excess weight loss of 8%. Pharmacotherapy has a very limited role in the treatment of adolescent obesity, compliance is often poor and drug choices are limited.

Studies of bariatric surgery highlight the potential weight loss that can be achieved in obese patients with the subsequent improved health, complication rates unfortunately remain high. In obese adolescents who fail to lose weight with lifestyle alone surgery is increasingly being considered. However there are currently no predictors to determine which adolescents will get complications from Laparoscopic Adjustable Gastric Banding or bypass surgery. Likewise there are no reliable predictors to determine which adolescents will have a good response from surgery, and there is no available

risk benefits data.

A less invasive option is the gastric balloon, achieving a temporary restriction of food intake in combination with lifestyle and behavioural changes the aim being to achieve long term weight loss. This has been achieved in adults with the use of a gastric balloon that floats in the stomach giving the individual the sensation of continued satiety, reducing their requirement and desire for food. While there have been large studies on the successful use of the BIB in obese adults. Only one small (n=5) retrospective study has been performed in adolescents with the use of the BIB. The purpose of this randomized clinical trial is to determine whether the use of the BIB aids weight loss in obese adolescents.

Specifically, that:

1. The BIB aids weight loss in obese adolescent patients.
2. The BIB will be well tolerated in obese adolescent patients.
3. The BIB will reduce the severity and frequency of obesity related co-morbidities in obese adolescents.

50 adolescent patients (male and female), age 12-17 years attending Princess Margaret Hospital (PMH) will be recruited to the study.

*Funding Source: NHMRC # 634308; Pfizer APEC Grant*

## RESEARCH RESOURCE REPOSITORIES AND DATABASES

TIM JONES; LIZ DAVIS

## TYPE 1 AND TYPE 2 DIABETES DNA BANK

INVESTIGATORS: TIM JONES; LIZ DAVIS

FUNDING SOURCE: DEPARTMENT OF ENDOCRINOLOGY & DIABETES, PMH

A prospective population-based diabetes register conforming to international standards, which stores demographic and clinical data on all patients attending the diabetes clinic at Princess Margaret Hospital for Children. The database also records family history, in the first degree relative, of autoimmune disease and atopic disease As PMH is the only tertiary paediatric referral centre in Western Australia, the case ascertainment of this register has consistently been over 99%. This complete, population-based data source is invaluable for studying the epidemiology of childhood onset diabetes in Western Australia.

## AUSTRALIAN CHILDHOOD DIABETES DNA REPOSITORY

INVESTIGATORS: GRANT MORAHAN; TIM JONES; LIZ DAVIS

STUDY STAFF: HEATHER ROBY

Both types of diabetes tend to run in families. This means that certain genes we inherit from our parents may increase or decrease the risk of developing diabetes.

By testing DNA samples from families affected by diabetes, we can identify genes which increase the risk of this disease. Identification of diabetes genes is important as it will help us to understand better why some people become diabetic, and help researchers to develop new treatments.

The Australian Childhood Diabetes DNA Repository (ACDDR) is aiming to collect DNA samples from Australian families affected by diabetes. Families with a child with either Type 1 or Type 2 diabetes are invited to participate. DNA for the Repository is collected once via saliva samples. To participate, both biological parents and the child with diabetes provide about a teaspoon of saliva in a special pot that we supply and can be collected in clinic or at home.

The Repository stores samples of DNA, so that Diabetes researchers, with the approval of relevant Ethics Committees, can then apply to access this Repository rather than asking your child and you for more blood samples.

*Funding Source: NHMR Enabling Grant*

## LONGITUDINAL TYPE 1 AND 2 DIABETES PLASMA AND SERUM REPOSITORY

INVESTIGATORS: TIM JONES; LIZ DAVIS

STUDY STAFF: ADAM RETTERATH

The Serum & Plasma bank was established to provide a store of samples from subjects with diabetes as well as their families. This resource will allow researchers to carry out scientific studies looking at the genetic causes for diabetes. The ultimate aim is to improve on current practice for prevention and monitoring of complications related to diabetes. Samples can only be accessed by research teams with appropriate ethics approval and sample details can only be accessed by authorised personnel.

*Funding Source: Internal Funds*

## WESTERN AUSTRALIAN CHILDREN'S DIABETES DATABASE

INVESTIGATORS: TIM JONES; LIZ DAVIS

This diabetes register was established at Princess Margaret Hospital (PMH) in 1987 which stores data on all consenting patients attending the hospital's diabetes clinic. In Australia, all children diagnosed with Type 1 diabetes (T1DM) are admitted to hospital at the time of diagnosis. As PMH is the only children's teaching hospital in Western Australia (WA), all children diagnosed with diabetes are seen by the diabetes department at this hospital. Since the diabetes register was set up, over 99% of children newly diagnosed with T1DM have consented to being registered in the register. This means that the register contains data on almost all children diagnosed with T1DM under the age of 15 years in WA, and can be used to accurately describe their characteristics.

A history of T1DM in the parents and siblings of children diagnosed with T1DM has been collected by the diabetes clinicians since 1992. Since 2005, this data collection has extended to include type 2 diabetes and other diseases associated with T1DM. This population based database for childhood is a valuable resource which will allow us to investigate the relationship between associated diseases may add to the understanding of their underlying mechanisms.

The data is collected using a questionnaire, either at the time of diagnosis for newly diagnosed patients, or during routine follow-up appointments, for patients attending the diabetes clinic. Data access will be restricted to relevant clinical and authorised research staff only. Consent is obtained from newly diagnosed

patients or their parents prior to the collection and storage of incidence data and family history data in the diabetes register. Patient confidentiality is maintained.

*Funding Source: Internal Funds*

## A DATABASE OF THE COMPLICATIONS OF OBESITY IN CHILDREN

INVESTIGATORS: LIZ DAVIS

STUDY STAFF: RACHELLE KALIC

The Obesity Database records the characteristics and medical complications of children with obesity who present to treatment at Princess Margaret Hospital, in an on-site database. The database records demographic and anthropometric data about participants in the study, as well as features of complications of obesity. Complications of obesity include an abnormal lipid profile, hypertension, glucose intolerance, fatty liver, musculoskeletal issues and obstructive sleep apnoea, among others. Analysis of this data quantifies the complications of obesity in children who are overweight and obese, and will be used to develop guidelines for investigation and treatment.

*Funding Source: Internal*

## WESTERN AUSTRALIAN DNA AND LONGITUDINAL SERUM BANK FOR WEIGHT REGULATION

INVESTIGATORS: LIZ DAVIS; TIM JONES; SUE BYRNE; JACQUELINE CURRAN;

STUDY STAFF: RACHELLE KALIC; ADAM RETTERATH

The establishment of this resource will allow

researchers in the future to carry out scientific studies which will look at the genetic causes of excessive weight gain (how excessive weight gain runs in families), and to identify biomarkers (special molecules) in blood that help predict individuals at risk of becoming overweight or at risk of developing obesity related diseases. Eventually the aim is to improve on current practice for prevention and monitoring of complications related to obesity.

The individuals that will be eligible for recruitment to the study will be overweight children their siblings and parents seen for their weight problem at Princess Margaret hospital, and families enrolled in the Growth and Development study through Institute of Child Health research.

DNA will be extracted from blood/saliva; serum & plasma from the blood samples. The samples collected will be coded so that no one outside the PMH research team will be able identify who the sample belongs to.

Fractions of DNA and protein results may be provided to properly qualified researchers, with PMH ethics approval, to identify susceptibility genes and biomarker results may be provided to properly qualified researchers, with PMH ethics approval, to identify susceptibility genes and biomarkers related to obesity and its complications.

*Funding Source: NHMRC Enabling Grant & Internal Funds*

## DISEASE SUBTYPES AND PHENOTYPE OF TYPE 1 AND TYPE 2 DIABETES

INVESTIGATORS: LIZ DAVIS



#### STUDY STAFF: HEATHER ROBY

Using Genome-Wide Association Study data produced by the Type 1 Diabetes Genetics Consortium (T1DGC), Prof Grant Morahan's team has found that the T1D can be grouped into six different disease subtypes. These sub-types appear to be associated with preponderance to particular co-morbidities of T1D and show a gender bias. This has recently been confirmed by analysis of the DNA samples provided to the Australian Childhood Diabetes DNA Repository (ACDDR). Furthermore, Prof Morahan's group has also found that type 2 diabetes (T2D) can be grouped into four genetically definable subtypes.

In order to further explore this finding, we propose to genotype a larger cohort of patients with T1D or T2D diagnosed below the age of 18y, to investigate the relationship between clinical traits and disease subtypes. This cohort will include all T1D and T2D cases who have consented to store DNA in the "T1D and T2D DNA Repository" (DNA Bank) of the Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Perth, Western Australia. Their DNA will be typed at over 40 genetic markers, which will allow each subject to be classed into one of the respective sub-types. Phenotypic data from all subjects will be retrieved from the "Western Australian Children's Diabetes Database" (WACDD) maintained by the Department of Endocrinology and Diabetes. This information will then be correlated with the corresponding disease subtypes.

This will potentially:

1. increase our understanding of the pathophysiology of T1D and T2D

2. allow us to identify those children most at risk of developing other autoimmune co-morbidities;
3. allow us to target diabetes management strategies specific to control and complication risk based on disease subtypes

*Funding Source: Internal Funds*

## Staff and Students (complete listing for Division required)

### HEAD OF DIVISION

Tim Jones; MBBS, DCH, FRACP, MD

Clinical Professor, The University of Western Australia

Practitioner Fellow, National Health & Medical Research Council

Head, Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children

Faculty Member - Senior Principal Investigator, Centre for Child Health Research, Telethon Institute of Child Health

Adjunct Professor, Institute for Health & Rehabilitation Research, The University of Notre Dame Australia

### SENIOR TEAM LEADER:

Liz Davis; MBBS, FRACP, PhD

Clinical Associate Professor, University of Western Australia

Head, Diabetes and Obesity Services, Princess Margaret Hospital for Children

Associate Professor, School of Paediatrics and Child Health, The University of Western Australia

Faculty Member - Senior Principal Investigator, Telethon Institute for Child Health Research, The University of Western Australia

### RESEARCH STAFF

Raymond Davey, PhD. Research Associate.

Megan Evans, APD, BSc, Post-Grad Dip (Nutrition and Dietetics). Dietitian.

Rachelle Kalic, BPsych. Research Officer.

Kaitie McNamara, BA(Hons). Research Assistant.

Jennifer Nicholas, BSc (Nursing), CDE, MSc (Diabetes Education) Research Nurse.

Nirubasini Paramalingam, HDip (Children's Nursing), Grad Cert (Diab Edu), BSc(Hons), Research Coordinator.

Adam Retterath, BSc(Hons). Research Assistant.

Heather Roby, BSc. Research Assistant.

Barbara Sheil, PhD. Clinical Trials Project Manager

Wayne Soon, BSc(Hons). Research Assistant.

Casey Lowden-Crook, BSc (Nursing). Research Nurse

### POSTGRADUATE STUDENTS

Matthew Cooper, BSc, PhD candidate. Biostatistician.

Aveni Haynes, BA(Hons), MBBChir, PhD candidate. Research Fellow.

### RESEARCH SUPPORT

Mary Flynn, Grad Dip(Counselling), BA (Fine Art). Administration Assistant.

### Awards

Tim Jones - 2012-2013 Novo Nordisk Fellowship

### External Committees

#### INTERNATIONAL

Liz Davis, Executive Council of Australasian Paediatric Endocrine Group

Liz Davis, Diabetes Database Committee – 2005 - 2012

Liz Davis, Diabetes Database Committee, Australasian Paediatric Endocrine Group. Member, 2005-

#### NATIONAL

Tim Jones, Member Scientific Review Committee Diabetes Australia Research Trust 2004-

Tim Jones, Member of Type 1 Diabetes Guidelines Expert Advisory Group.

Tim Jones, Chairman Australian Paediatric Endocrine Council Research Grant Review Body.

Tim Jones, Diabetes & Endocrine Health Networks Advisory Group – Member 2011-2012

Tim Jones, JDRF – Type 1 Diabetes Clinical

Network Steering Committee

Tim Jones, JDRF Clinical Trials Network – Spokesperson

Tim Jones, NHMRC Research Translation Faculty – Member

Tim Jones, Telethon Juvenile Diabetes Parents' Centre – Board Member

Liz Davis, Australian Paediatric Endocrine Council Research Grant Review Body. Chairman 2011-2012

Liz Davis, SAC Endocrinology, RACP, Member 2010-2012

Liz Davis, Executive committee of Australian Tertiary Obesity Clinical Network. Member 2009-

Liz Davis, Endocrine training and curriculum development subcommittee, APEG, Member, 2009-

Liz Davis, Advisory member of Birth Defects Registry. Advisory Member, 2004-

## LOCAL

Tim Jones, Member Medical Advisory Panel, Diabetes Research Foundation of Western Australia 2002-

## Invited Presentations

Tim Jones, Plenary Speaker. Insights into the Future of Glucose Management - Managing Hypoglycemia: a prospective view of GCM technologies. at 5th International Conference, Advanced Technologies & Treatments for Diabetes, Spain. Feb 2012.

Tim Jones, Invited Speaker, CME Symposium: Waiting for Closed Loop – tapping the full potential of advanced diabetes technology in today's clinical practice. American Diabetes Association, 72 Scientific Sessions, Philadelphia PA, USA June 2012.

Tim Jones, Plenary Speaker. Technology in Diabetes Therapy. Australasian Paediatric Endocrine Group: Annual Scientific Meeting, New Zealand, July 2012.

Tim Jones, Invited Speaker. Artificial Pancreas: Myth or Reality? Australian Diabetes Educators Association WA Branch Conference, Perth, May 2012.

Tim Jones, TW. Invited Speaker. Numbers: Use of data in Diabetes Management and Clinical Research. Melbourne & Sydney, May 2012.

Tim Jones, Invited Speaker. Exercise and its prevention in Type 1 Diabetes. "Directions in Diabetes" Symposium. Sydney, May 2012.

Tim Jones, Invited Speaker. Regional Differences in Paediatric Diabetes. "Directions in Diabetes" Symposium. Sydney May 2012.

Tim Jones, Invited Speaker, Tots and Technology. NHMRC Clinical Trials Centre Master Class, 4th Update on Diabetes & Vascular Disease Sydney July 2012.

Invited Speaker: Use of data in diabetes therapy. Tim Jones, Australian Paediatric Society: Plenary Talks, July 2012.

Tim Jones, Invited Speaker: Preventing nocturnal hypoglycaemia. Australian Paediatric Society: Plenary Talks, July 2012.

## ACTIVE collaborations

A/Prof Maria Craig: Australian Clinical Trials Network; NSW

Prof David Dunger: Addenbrooke's Hospital, Cambridge, UK

Dr Dennis Daneman: Hospital for Sick Children, Toronto, Canada

Prof Paul Fournier: School of Sports Science and Exercise Health, UWA

Winthrop Prof Danny Green: School of Sports Science and Exercise Health, UWA

Prof Grant Morahan: Western Australian Institute for Medical Research

Mr Sean Gray: AIMedics Pty Ltd, NSW

Prof Hung Nguyen: University Technology, Sydney, NSW

Winthrop Prof Mike Anderson: School of Psychology, UWA

Dr Lim Ee Mun: Clinical Biochemistry, PathWest, Sir Charles Gairdner

# DRUG DISCOVERY

## Overview

### THE DRUG DISCOVERY TECHNOLOGY UNIT AND ITS COMMERCIALIZATION VEHICLE PHYLOGICA LTD.

The Drug Discovery Technology Unit (DDU) is focused on developing therapeutic approaches against disease-associated protein interaction targets both inside and outside of cells as well as the development of 'mimetic' vaccines against discontinuous epitopes. The research of the unit is funded by contracts with large pharmaceutical companies via a commercial entity named 'Phylogica' which was the first spin-off company from the Telethon Institute for Child Health Research.

Phylogica (<http://www.phylogica.com>) is a specialist drug discovery company, which identifies new prototype drugs for large drug company customers. It achieves this by drawing from its own huge source of billions of unique compounds from nature, the world's largest and most diverse collection (see below). These peptides are strongly protected by a portfolio of more than 10 patent families, including granted patents in the US and Europe. The peptide drug class which Phylogica controls access to is known as "Phylomers". Since December 2009, Phylogica has done deals with four pharmaceutical companies around access to this new class of peptides (Roche, MedImmune/Astra Zeneca, Pfizer and Janssen).

### PHYLOMERS: A STRUCTURALLY DIVERSE LIBRARY OF PEPTIDES DERIVED FROM PROTEIN FRAGMENTS ENCODED BY

## BIODIVERSE GENOMES

Phylogica's proprietary Phylomer® libraries represent a rich source of biologically active drug leads for a broad range of intracellular and extracellular disease targets. The Phylomer libraries are based on expressed protein fragments that are encoded by the genes of evolutionary diverse microbes. These microbes often exist in extreme environments such as deep sea volcanic vents and geysers. Typically, these peptides, which are known as Phylomer peptides, are comprised of 15 to 50 amino acids. The inherent diversity of the genetic sources of Phylomer peptides means that libraries contain multiple classes of subdomain and supersecondary structures across thousands of distinct structural families. Phylomer peptides can show excellent specificity and can function as high affinity disruptors of protein-protein interactions and binders of protein targets.

Since Phylomer libraries represent the most comprehensive collection of protein-based peptide structures available, this gives them a significant advantage over other peptide libraries of random amino acid composition. This feature of high structural diversity, has resulted in Phylomer® libraries successfully yielding high quality functional primary hits (pM-nM affinity), against multiple classes of intracellular and extracellular drug targets, as well as in direct phenotypic screens. Phylomer libraries have a number of advantages against a range of alternate random peptide screening technologies for biologic discovery. This leads to their versatile application in a range of distinct areas.

THE SUPERVISOR OF ALL LABORATORY RESEARCH IS THE DDU PROGRAM MANAGER:

DR RICHARD HOPKINS

## UPGRADES TO THE PHYLOMER LIBRARIES

PROJECT LEADER: DRS NADIA MILECH WITH DRS KATRIN HOFFMANN, ASSISTED BY ROB DEWHURST, LAURA FLOREZ, MARIE SCOBIE, MARK ANASTASAS AND CLINTON HALL.

The DDU has vastly upgraded the complexity of its Phylomer libraries, which now comprise over 170 billion distinct peptides across multiple display formats using the complementary M13 and T7 phages. The new libraries have been made with an optimized set of microbial genomes which both span a greater diversity space. Libraries have also been constructed from a focussed set of bacterial and viral genomes from pathogenic species, which have tropisms for particular tissues. These libraries will enhance the DDU's proven capability in isolating tissue specific cell penetrating peptides corresponding to parts of natural virulence factors which have evolved for cell invasion. In addition, the DDU has been constructing focused libraries, which are further enriched for likelihood of discovering structured peptides. This approach has increased the number of productive read-through clones from 15 to 86% while also improving the proportion of natural open reading frames.

## EXTRACELLULAR TARGETS

### BLOCKING THE INFLAMMATION TARGET CD40 LIGAND (CD40L)

LED BY DR PAULA CUNNINGHAM ASSISTED BY DR SHANE STONE, THERESA CONNOR, MARIA KERFOOT, YEW FOON TAN, SCOTT WINSLOW

The CD40L receptor on T-cells is critical for many inflammatory diseases, including Asthma, Inflammatory Bowel Disease, Rheumatoid arthritis and Lupus erythematosus. We have identified potent Phylomers, which are able to block the interaction between CD40L on T-cells and CD40 on antigen presenting cells or on B-cells. These new lead compounds are currently being fast-tracked into animal models of disease to determine their biological activity and potency - key end points of interest to the large pharmaceutical companies, who are considering licensing these compounds for inflammatory diseases.

We have identified more than 25 leads which were chosen for their drug like properties, their affinity for the CD40 Ligand. Nine of these leads specifically blocked the CD40/CD40L interaction and seven of these CD40L hits were amenable to ortholog scanning (28%) as they correspond to conserved folds in the protein structure databases.

## DISCOVERING NEW ANTIMICROBIALS AGAINST MULTI-RESISTANT MICROORGANISMS

PROJECT LEADER: TATJANA HEINRICH BSC (HONS), PHD ASSISTED BY SARAH SEE AND TRACY CHAI.

The Drug Discovery Technology Unit has had extensive experience in the discovery of antimicrobial peptides from its phylomer libraries. Some of these peptides have activity on multiresistant isolates of *Acinetobacter baumannii*, an important cause of hospital acquired infections of burns patients. We have also screened Phylomer libraries to identify and

characterize antimicrobial peptides against the related pathogen *Pseudomonas aeruginosa*, which is involved in hospital-acquired catheter and burns infections as well as lung infection, particularly in children suffering from cystic fibrosis. The group has investigated the secondary structure of antimicrobial Phylomer peptides by a technique known as circular dichroism. These studies measure the extent of formation of alpha helix structure in model membranes incorporating various phospholipid mixtures which mimicking different types of bacteria or mammalian cells. These studies found good agreement between prediction *in silico* and biophysical measurements. We also were able to optimize antimicrobial Phylomer peptides - reduced length to approximately 20 amino acids and improving the antimicrobial activity (MIC) to the high nanomolar range. Recent studies have explored the potential synergy between clinical antibiotics and antimicrobial Phylomer peptides and found at least one potent combination. We have found a number of peptides with antimicrobial activity against the nosocomial infective agent *Pseudomonas aeruginosa*. We have established a control panel of recently published, highly active natural antimicrobial peptides and compared them with antimicrobial Phylomer peptides under different salt conditions (different growth media), and have identified Phylomer derivatives which are more active than a potent antimicrobial peptide known as Tachyplesin which is isolated from the horse-shoe crab.

The collaboration with MedImmune, the worldwide biologics unit of AstraZeneca, was announced in August 2010. The overall aim

was to use our Phylomer® libraries to discover novel antibiotic agents to treat various bacterial infections. The key target organism is multi-drug resistant *Pseudomonas aeruginosa*, which is a major cause of hospital-acquired infections and is also the main cause of lung problems in Cystic Fibrosis sufferers. In this project we identified approximately six AMPs with activity in *A. baumannii* and *Klebsiella* and *P. aeruginosa*. One of the peptides adopted a beta-sheet structure according to circular dichroism and screening a few shortened versions of these peptides resulted in identification of a 15mer with an MIC of 1.8µM in *A. baumannii*. Encouragingly many of these peptides are active on clinical isolates and show no evidence of toxicity against mammalian cells, unlike many conventional AMPs.

In summary we have identified multiple Phylomers with antimicrobial activity against the target organism *Pseudomonas aeruginosa*, as well as candidates which also have activity against clinical isolates of important nosocomial pathogens such as *Acinetobacter*, *Klebsiella* and *Staphylococcus*, while not exhibiting toxicity. We continue to work on the optimisation of these peptides.

## THERAPEUTIC VACCINE DEVELOPMENT

### SCREENING PHYLOMER LIBRARIES FOR MIMOTOPES OF DISCONTINUOUS OR CONFORMATIONAL EPITOPES ON AN ANTIGEN FOR THERAPEUTIC VACCINATION

PROJECT LEADER: DR KATRIN HOFFMANN

ASSISTED BY SUZY JURAJA, SUSAN TURNER, SCOTT WINSLOW, MARK ANASTASIS, YEW-FOON TAN.

In December 2011, the DDU began working on a collaboration with Pfizer to discover novel peptide-based vaccines. This collaboration was based on the structural richness of Phylomer libraries, which make them more suitable than random peptide libraries for the discovery of peptide mimetics of discontinuous epitopes. Such epitopes are commonly found to be the most 'immunologically fit' in eliciting efficient B-cell responses and therefore are believed to be a good source of vaccine candidates.

Phylomer libraries were screened against two distinct antibody targets that recognised a therapeutically relevant antigen and multiple vaccine candidates were identified. It was then required to fuse the Phylomers to a virus-like particle in order to make them immunogenic. Immunisation with such Phylomer fusions was found to elicit an antibody response, which was specific for the target antigen. The properties of these Phylomer peptides have led to Phylogica achieving a discovery milestone, leading to Pfizer taking more than 25 of these peptides for internal evaluation in animal models as vaccine candidates.

## INTRACELLULAR TARGETS AND NOVEL DELIVERY APPROACHES

### DISCOVERY AND CHARACTERISATION OF NOVEL CELL PENETRATING PHYLOMERS

PROJECT LEADER: DR KATRIN HOFFMANN

BSC (HONS), PHD ASSISTED BY DRS PAULA CUNNINGHAM, NADIA MILECH, SUZY JURARA AND KAREN KROEGER AS WELL AS BY MARIA KERFOOT, THERESA CONNOR, SUSAN TURNER, BROOKE LONGVILLE, HEIQUE BOGDAWA, MARK ANASTASIS AND CLINTON HALL.

The emerging field of cell penetrating peptides (CPPs) is generating considerable excitement in the pharmaceutical industry. Not only can this class of peptide be used to deliver existing drugs inside cells but they also provide access to an entirely new landscape of intracellular targets. Indeed, estimates suggest that 80% of 'druggable' targets are located inside cells. Combined with the fact that CPPs can deliver new classes of drugs such as biologics into cells, one can appreciate why CPPs have the potential to significantly expand the landscape of targets currently considered druggable.

Phylogica has screened its Phylomer libraries to identify peptides that can deliver drugs into cells. These efforts yielded approximately 1000 unique candidates, highlighting the structural and functional diversity present within our Phylomer libraries. After screening a sub-pool of 166 Phylomers, a total of 17 peptides were confirmed as having cell penetrating activity, corresponding to a functional hit rate of 11%.

Most importantly, our recent analysis has identified multiple classes of novel cell penetrating Phylomers. These peptides range from the traditional short, positively charged CPPs, to novel negatively charged Phylomer peptides that mimic invasive viral peptides which are involved in cell entry and escape into the cytoplasm of the pathogens in which they evolved. For example, the sequence of one of our novel cell penetrating Phylomers is

analogous to a viral peptide found in the Simian Immunodeficiency Virus (SIV). We have also identified cell specific Phylomer® peptides and others that are aligned to bacterial virulence factors known to be involved in cell invasion (for example: the fibronectin binding protein from *Staphylococcus aureus*).

We have also identified CPP's which are specific for particular cell types such as brain endothelial cells. Our ability to enrich for different classes of peptides with natural cell penetrating activity specific for particular tissues is unique to our Phylomer technology and has generated considerable interest with prospective Pharma partners.

Phylogica is currently developing a second generation screening platform, designed to improve significantly on the diversity and quality of cell penetrating Phylomers that can be isolated, since it allows the specific capture of those CPP's which have escaped from the endosome to enter the cytoplasm or nucleus where their cargoes can act on targets.

## INTRACELLULAR PROJECTS AND TARGET DISCOVERY

### ANTICANCER PHYLOMERS: TARGETING INTRACELLULAR 'SONIC HEDGEHOG' PATHWAYS.

NADIA MILECH BSC (HONS), PHD HEAD OF INTRACELLULAR PROJECTS AND TARGET DISCOVERY FOR THE DDU ASSISTED BY BROOKE LONGVILLE AND MARIE SCOBIE IN COLLABORATION WITH JULIUS VARANO, PETER DALLAS BSC (HONS), PHD AND NICK GOTTARDO BSC (HONS) PHD FMEDSCI, HONDSC,

(CANTAB) OF THE DIVISION OF CHILDREN'S LEUKAEMIA AND CANCER RESEARCH

Inappropriate inactivation of the 'Sonic hedgehog' (SHH) pathway causes cancer and is associated with malignancies such as basal cell carcinoma (a form of skin cancer) and a childhood brain cancer known as medulloblastoma. By targeting this pathway we aim to identify Phylomer peptides as potential anti-cancer therapeutics in these diseases. Resistance is already emerging to a small molecule drug in this area developed by Curis/Genentech. We believe that a Phylomer approach against alternative targets in this pathway will help address this resistance issue, while exploiting the encouraging efficacy seen with blockade of SHH.

Screens of our Phylomers against two independent targets in the Shh pathway have yielded over 100 potentially interesting, unique peptides. Approximately 25% of hits against each target were functionally active in an industry-standard reporter-gene bioassay we have adapted for high-throughput intracellular targeting validation. These bioactive Phylomers are being independently assessed in a highly validated differentiation assay, to identify the optimal lead candidates for further development. Initial results have been very promising and shown that the most effective Phylomer peptides in the reporter assay are also showing activity in the biological differentiation assay.

These Phylomer leads will be further evaluated to determine their suitability for assessment in a predictive preclinical *in vivo* model of medulloblastoma that has been established by our collaborators within the Brain Tumour

Group at the Telethon Institute of Child Health Research.

### PHENOTYPIC SCREENING FOR TARGET DISCOVERY & VALIDATION

PROJECT LEADERS A PROF PAUL WATT, DR NADIA MILECH AND DR RICHARD HOPKINS, IN COLLABORATION WITH CAMBRIDGE UNIVERSITY)

The Drug Discovery Technology Unit has been collaborating with Ashok Venkitaraman, the distinguished Professor of Oncology of the Hutchison MRC Unit at the University of Cambridge in the UK.

The objective of this collaboration has been to test if Phylomer libraries might assist in identifying new cancer targets for the discovery of new drugs. The Hutchison group has shown the Phylomers can bind to defined targets linked to cancer cells, and that the hit-rate in a phenotypic mammalian screen of a Phylomer library is superior to that from traditional approaches used by pharmaceutical companies.

Having achieved this aim, the next relevant step was to use the target binding as a tag to identify the key biological step in a pathway for which new drugs might be built. The success of the target identification using the Phylomers in this collaboration highlights the usefulness of this approach for target discovery.

It has subsequently been shown that a Phylomer can be used not only to identify a candidate target, but also to validate that target via 'protein interference'. It is expected that this target validation at the protein level, will be very useful as it provides an opportunity to block

disease-relevant interfaces of target proteins while not blocking their normal functions.

## Staff and Students

### HEAD OF DIVISION PRINCIPAL PROGRAM MANAGER

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CEO of Phylogica Ltd

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Paul Watt BSc.(Hons) D.Phil (Oxon)

University of Western Australia, 'Pathfinder' commercialization

Richard Hopkins, BSc. (Hons) PhD

Ausbiotech, Western Australian Committee

## Invited Presentations in 2012

Adjunct Professor Paul Watt

30th Annual JP Morgan Healthcare Conference

9 - 12 January 2012 San Francisco (CA), USA

14th Annual BIO CEO & Investor Conference

13 - 14 February 2012 New York (NY), USA

2012 BIO International Convention

18 - 21 June 2012 Boston (MA), USA

Next Generation Protein Therapeutics Summit

25 - 27 June 2012 San Francisco (CA), USA

Proteins & Biopharma Asia Congress

Proteins & Biopharma Asia Congress 10 - 11 September 2012 Singapore

Sofinnova Japan Partnering Conference

30 October 2012 Tokyo, Japan

BIO-Europe 2012

12 - 14 November 2012 Hamburg

Dr Richard Hopkins

EuroPhages2012

EuroPhages2012 24 - 26 September 2012 Oxford UK

Oxford Global 2nd Annual Next Generation Sequencing Asia Congress

01 - 02 October 2012 Singapore

EuroPEPTIDES 2012

27th - 28th Nov 2012 Berlin

BioPharm Australasia Convention 2012

23 - 24 August 2012 Sydney, Australia

Dr Shane Stone

Phage & Yeast Display of Difficult Targets

Molecular Med Tri-Con 19 - 20 February 2012 San Francisco (CA), USA

32nd European Peptide Symposium 7 September 2012. Athens

Dr P Cunningham and Prof Watt

IBC Oligonucleotide and Peptide, Research, Technology and Product Development (TIDES) 20 - 23 May 2012 Las Vegas (NV), USA

Dr Nadia Milech, Tatjana Heinrich and Prof Watt

Eighth Annual PEGS Summit, April 30th- May 4th, Boston

## Active Collaborations

Professor Ashok Venkitarman, Cambridge University (Hutchison MRC Research Institute), Phenotypic screening and target identification

Professor Greg Weiss, University of California at Irvine CA, USA

Protein Engineering and lead optimization strategies.

Associate Professor Marie Bogoyevitch, University of Melbourne (Bio21 Institute), VIC

Adjunct Associate Professor Bruno Meloni and

Professor Neville Knuckey

Australian Neuromuscular Research Institute, WA. Neuroprotective Phylomers targeting the AP1 pathway

# GENETICS & HEALTH

## Overview

Our research is applying genomics and metabolomics to understand complex diseases, helping us to find better diagnostics and vaccines. Modern research tools allow us to look at all of our genes and metabolic products to identify biomarkers of complex diseases like infections and diabetes. With the advancing obesity plague, WHO estimates that nearly 350 million people world-wide have diabetes, and the problem is increasing in children. Diabetes is a major risk factor for infectious diseases like tuberculosis and sepsis, as well as cardiovascular, neurological, and kidney diseases.

In Australia, we are investigating the genetic basis to diabetes and extreme outcomes like end-stage renal disease in a Western Australian Aboriginal population. In south-east Asia and Northern Australia, there is a particular association between diabetes and sepsis, and people who have a specific form of sepsis caused by melioidosis are more likely to die quickly. Our work in Thailand has permitted us to identify several metabolic biomarkers that predict which individuals have this form of sepsis so that they can be treated early with appropriate therapy that will reduce the risk of death. We are now extending those studies to look at melioidosis in Australia.

Our group leads international consortia that are using genetics and metabolomics to understand infections of resource-poor nations, especially for a disease called leishmaniasis, in India, Brazil and Sudan, and fevers caused by bacterial infections and malaria in Africa. A particular need in Africa is to be able to rapidly diagnose the cause of fever in children, and

metabolomics is being used to identify rapid diagnostic biomarkers especially for bacterial infections. In the case of life-threatening visceral leishmaniasis, the major effort is focused on research that could aid in vaccine development. There are no vaccines in routine use against this disease, and there is a particular need to ensure that next generation defined vaccines will be effective even in genetically susceptible individuals. This year we published our major findings in *Nature Genetics* on the role of HLA Class II molecules in determining susceptibility to visceral leishmaniasis. The significance of this finding is that **we have determined that the most important genetic risk factor for visceral leishmaniasis lies at the heart of eliciting T cell immunity**. By understanding the specifics of antigens presented to the immune system by protective versus risk-associated HLA Class II molecules, we are in the best position ever to design a vaccine(s) that will subvert the inappropriate immune response normally made by a susceptible individual encountering infection for the first time, and transform this into a protective outcome.

Childhood diseases in Australia are also a major focus of our research. Ear infections leading to otitis media are the most common reason for young children to visit a doctor, and are a major cause of burst eardrums and deafness in Aboriginal children. Our work has led to several publications over the last year highlighting the role of specific genes in determining susceptibility to otitis media in Western Australian children. We are also interested in congenitally acquired diseases, including the outcomes of infections such as toxoplasmosis transmitted to babies *in utero*,

as well as developmental anomalies such as hypospadias. Toxoplasmosis is caused by a ubiquitous parasitic infection with the most severe clinical signs observed in babies infected early in pregnancy, and we have exciting new data demonstrating that the parasite itself secretes proteins that influence how the host cell functions. Hypospadias is the second most common birth defect in boys, and our research is looking at why some boys are born with hypospadias, with a focus on any genes that are involved as well as how the genome interacts with environmental factors which change gene expression by mechanisms other than changes in the underlying DNA code, i.e. through epigenetic (“above genetics”) mechanisms.

## Genetics of complex disease

### FAMILY STUDY OF EAR HEALTH AND METABOLIC DISEASES IN A WESTERN AUSTRALIAN ABORIGINAL COMMUNITY

JENEFER M BLACKWELL, SARRA E JAMIESON, HEATHER J CORDELL, DENISE ANDERSON, MICHAELA FAKIOLA, ELIZABETH S H SCAMAN, ELIZABETH DAVIS, HARVEY L COATES, SHYAN VIJAYASEKARAN

A family-based study of ear health and metabolic diseases has been underway since 2008 with the full support of the Aboriginal community serviced by the Ngangganawili Aboriginal Health Service (NAHS). A Memorandum of Understanding was established between NAHS and TICHR, and the study was approved by the Western Australian Aboriginal Health Ethics Committee (WAAHEC). Over the course of the project we drew up pedigree structures for the

entire study population, and extracted trait data from the clinical records. We completed 2.5M Illumina Duo SNP-chip analysis of the >400 post-QC individuals for whom a consented DNA sample was obtained and undertook genome-wide association analyses for type 2 diabetes, body mass index, and other related clinical traits. Analysis of data for otitis media phenotypes is in progress. In addition, we re-sequenced the top candidate genes (from other global studies) for obesity and type 2 diabetes using Sanger sequencing on 95 affected individuals and found no obvious deleterious variants consistent with the results of the GWAS. We carried out exome sequencing on 72 individuals to identify potential functional variants in the genes shown to be associated with metabolic disease traits in our study population, and to search for deleterious variants associated with extreme phenotypes such as end stage renal disease. Further analysis of these data is in progress. We engaged with community to provide information and feedback in culturally appropriate formats, including an art-based community educational project for feedback of scientific results and production of an animation that is available on YouTube as “The Goanna and the Journey of the Genes” (Martu and English versions). Clinical investigators on the project complemented clinical care by undertaking additional specialist clinics. All data from these specialist visits was recorded in the NAHS Communicare records for local clinical use. We have provided feedback of scientific findings to the Board of NAHS, comprising Elders from all major families within the study population, and obtained their permission for publication of results in scientific and medical journals. In brief, we initiated one of the first projects to successfully bring modern

genomics to aid in understanding the burden of disease in Aboriginal Australians. Details of results are under pre-publication embargo, as per our memorandum of understanding with the community.

*Funding:*  
NHMRC

## UNDERSTANDING LEISHMANIASIS THROUGH HLA

JENEFER M. BLACKWELL, MICHAELA FAKIOLA, JOYCE OOMMEN, TOOLIKA SINGH, SHYAM SUNDAR

In a recent (*Nature Genetics*, 2013, 45:208-213) genome-wide association study (GWAS) we identified HLA DRB1 allele groups tagged by ancestral haplotypes that confer disease risk (DRB1\*11/\*13/\*14 allele groups), or protect (DRB1\*15/\*16/\*01 allele groups) from, human visceral leishmaniasis in India and Brazil (Combined  $P=2.76 \times 10^{-17}$ ,  $OR=1.41$ , 95%CI 1.30-1.52). One mechanism to account for this association is that the top single nucleotide polymorphisms (SNPs) associated with visceral leishmaniasis tag polymorphisms in regulatory elements that affect classical Class II gene expression. Alternatively, or in addition, the top SNPs could tag variants that determine functional differences at the amino acid level which directly influence epitope selection and antigen presentation. To address the former, *in silico* interrogation of regulatory elements upstream of the DRB1 gene has identified key regulatory elements that differ between risk versus protective haplotypes that have now been cloned into reporter gene constructs for functional evaluation. To address the latter, two

transgenic lines of mice are being created with genOway in which the endogenous IA class II molecule in H-2<sup>b</sup> haplotype mice is replaced with a cistronic construct containing specific DRB1 (\*1404 risk vs \*1501 protective) and DRA cDNA sequences separated by an IRES and expressed under the endogenous MHC class II IA gene promoter, in mice chimeric for extracellular domain humanized CD4. In addition, naturally processed leishmanial peptides are being purified from EBV transformed B cells prepared from homozygous HLA DRB1\*14 versus HLA DRB1\*15 donors stimulated with whole crude parasite lysate prepared from a local Indian strain of *L. donovani*. Mass spectrometry is being used to identify these naturally processed peptides and compare the results with *in silico* predictions of epitopes and binding affinity.

*Funding:*  
NIH Tropical Medicine Research Centre (Leader S Sundar, India; Project leaders J M Blackwell and M Fakiola)  
NIH RO1 (Joint-PIs J M Blackwell, TICHR and M E Wilson, Iowa, USA)

## CANDIDATE GENE AND GENOME-WIDE STUDIES FOR OTITIS MEDIA

SARRA E JAMIESON, MARIE S RYE, ELIZABETH S H SCAMAN, RICHARD W FRANCIS, HARVEY L COATES, SHYAN VIJAYASEKARAN, SELMA P WIERTSEMA, RUTH B THORNTON, CRAIG E PENNELL, ANGELICA NGUYEN, LEA-ANN KIRKHAM, STEVE BROWN, MAHMOOD BHUTTA AND JENEFER M. BLACKWELL

Otitis media (OM; or ear infections) is the most common illness-related reason for a visit to a medical practitioner by preschool children, for paediatric antibiotic use, and for surgery in

childhood. Whilst 80% of children will suffer at least one episode of OM at some time before school age, around 40% will suffer from recurrent or chronic episodes of OM (i.e. severe OM) leading to an increased risk of conductive hearing loss, delayed language development and poor educational outcomes. Current medical and surgical treatments for OM are suboptimal and preventative interventions, such as vaccines, have had very limited impact to date. It is known that susceptibility to OM has a genetic component but the genes underlying this susceptibility are currently poorly described.

To determine the genes that play a role in childhood susceptibility to severe OM we established the Western Australian Family Study of OM. This study has recruited over 1000 children diagnosed with severe OM that required the surgical insertion of grommets. Using these samples along with data available from the Western Australian Pregnancy (Raine) Cohort we have identified several genes that play a key role in susceptibility to OM. This includes several genes that fall within the TGF $\beta$  and hypoxia pathways. This suggests that these two essential biological pathways play an important role in the development of OM and we are now following up the results of our genetic studies with functional analyses to determine the exact role of the genes involved.

*Funding:*  
The Raine Foundation  
Brightspark Foundation Fellowship  
UWA Research Development Award

## Metabolomics for infectious diseases

### METABOLOMICS APPLIED TO EMERGING INFECTIOUS DISEASES

JENEFER M. BLACKWELL, SASKIA DECUYPERE, GANJANA LERTMEMONGKOLCHAI, SUNE KORBRSISATE

Metabolomics is a new biomedical discipline that permits rapid detection of a person's metabolic 'abnormalities' indicating infection or disease, by analyzing a simple blood or urine sample. This frontier technology could lead the way to new diagnostic solutions for infectious diseases that thwart the current diagnostic arsenal. Our project critically evaluates metabolomics as a new diagnostic strategy for the lethal disease melioidosis, which is endemic and on the rise in tropical Australia.

*Funding:*  
NHMRC

### A NOVEL APPROACH TO ADDRESS THE DIAGNOSTIC CONUNDRUM OF SEVERE FEBRILE ILLNESS IN AFRICAN CHILDREN

SASKIA DECUYPERE, JONATHAN CARAPETIS, STEVE GRAHAM, JAN JACOBS, TINTO HALIDOU

Acute fever is one of the leading causes of hospitalisation and death in children in the tropics and subtropics. Whilst malaria is traditionally perceived as the major cause, tropical childhood fevers more often result from non-malaria infections. Current tests for these infections are limited and often result in missed diagnoses or death. Our research uses emerging metabolomics technologies to develop simple



tests to better identify and treat these serious diseases.

*Funding:*  
Telethon Institute for Child Health Research  
Small Grants

## Epigenetic factors in congenital disease

### TOXOPLASMA PARASITES AND EPIGENETIC REGULATION OF HOST GENE EXPRESSION

SARRA E JAMIESON, GENEVIEVE SYN, RICHARD W FRANCIS, MARIE SIM AND JENEFER M. BLACKWELL

*Toxoplasma gondii* is a ubiquitous, intracellular, protozoan parasite. Up to a third of the world's human population is estimated to carry a *Toxoplasma* infection. For women who acquire infection for the first time during pregnancy, approximately 25% transmit the parasite to their foetus. Between 0.1/1000 to 1/1000 live born babies have congenital toxoplasmosis, with the highest rate reported in France, Eastern Europe and Brazil. In Australia, the seropositivity rate amongst women attending antenatal clinic is 23%, compared to ~50% in India and Brazil. Transmission risk is determined by the gestation at maternal infection, ranging from 5% for women who seroconvert at 12 weeks gestation to 80% if seroconverting just before delivery. At birth, 10% of infants infected *in utero* have intracranial calcifications, 4% hydrocephalus, and 10% develop ocular lesions (retinochoroiditis). New ocular lesions can occur at any age after birth with 20% of children acquiring ocular lesions by age 6 and 50% by adolescence. Up to

half of these children will have permanent visual impairment. Of particular interest, **the most devastating clinical outcomes are observed when pregnant women become infected for the first time very early in pregnancy, when the host epigenome is being reprogrammed.**

In our research we have demonstrated that *T. gondii* modifies epigenetic regulation of mammalian host genes. Specifically that infection of EBV-transformed B cells reverses epigenetically determined mono-allelic expression of paritular genes, *ABCA4* and *COL2A1*, that we had shown previously were genetically associated with clinical signs in babies born with congenital toxoplasmosis. To determine if these epigenetic changes are mediated by the parasite itself we have also carried out a computational analysis of all proteins known to be secreted from the *T. gondii* parasite during infection to identify which could be targeted to the host nucleus. Our results revealed 35 proteins that are secreted by *T. gondii* into the host cell which contain signals or motifs that could target them to the host cell nucleus. Of these proteins, 24 were shown to have protein domains consistent with an epigenetic function. For example, we identified several proteins capable of modifying histones, including a histone acetyltransferase and a histone methyltransferase, as well as protein capable of altering DNA methylation. To follow this up we are now undertaking functional analysis of these parasite proteins and their localization within the host cell during infection. We are also using cellular models *in vitro* and murine models *in vivo* to uncover the mechanisms by which *Toxoplasma* interferes with epigenetically regulated host gene

expression. Expression profiling undertaken in parallel with analysis of global epigenetic signatures will provide important and novel information about how *Toxoplasma* parasites influence pathological changes in the host.

*Funding:*  
UK Guide Dogs for the Blind

### UNDERSTANDING HYPOSPADIAS

SARRA E JAMIESON, NATASHA NASSAR, GENEVIEVE SYN, NAJEE FAYAD, ANDREW BARKER, NAEEM SAMNAKAY AND ANDREW HOLLAND

Hypospadias is a clinically significant birth defect in boys that is characterised by an abnormal position of the urethral opening. Instead of opening at the tip of the glans penis the urethral opening is on the ventral (or underside) surface of the penile shaft, scrotum or perineum. Hypospadias is accompanied by the incomplete development of the foreskin and is associated with a long-term risk of male sub-fertility, reduced semen quality and testicular cancer. Our analysis of data from the Western Australian population shows hypospadias to be the second most common birth defect in boys, affecting 1 in every 130 male infants, and reveals that rates have doubled over the last 25 years. The majority of hypospadias cases are thought to arise due to disruption of male hormone levels/action during development but the molecular mechanisms underlying this birth defect have not been well characterised.

To allow a comprehensive analysis of the molecular mechanisms that contribute to hypospadias we established The Understanding Hypospadias Study in WA in 2009 and in NSW

in 2010. This study is based at the Telethon Institute for Child Health Research. As part of this study we are currently analyzing gene expression and epigenetic profiles of samples from boys diagnosed with hypospadias compared to boys without hypospadias. Our results have revealed altered gene expression and DNA methylation profiles in hypospadias tissues, advancing our understanding of the underlying disease mechanisms.

*Funding:*  
Telethon Institute for Child Health Research  
Small Grants  
UWA Research Development Award  
Cancer Council WA

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Marie Sim, BSc, Honours student

Toolika Singh, BSc (Hons), MSc – PhD (Banaras Hindu University, India)

Genevieve Syn, BSc (Hons), PhD Candidate (P/T)

## RESEARCH SUPPORT

Joyce Oommen, MSc

Genevieve Syn, BSc (Hons)

## AFFILIATED MEMBERS OF THE DIVISION

Mr Richard Francis, Senior Bioinformatician

Ms Denise Anderson, Biostatistician

Dr Michaela Fakiola, Visiting Raine Fellow, Cambridge Institute for Medical Research

A/Prof Christopher Peacock, UWA, Team leader for Pathogen Genetics

Ms Choo Yu Leng, UWA, Research Assistant, Pathogen Genetics Team

Mr Wei Lu, UWA, Research Officer Bioinformatics, Pathogen Genetics Team

Dr Calila Santos, UWA, PhD Candidate, Pathogen Genetics Team

## Awards

Saskia Decuypere:

Winner – TICHHR presenter of the month November 2012

Runner-up – TICHHR presentation of the year 2012

Travel award from Friends of the Institute of Child Health Research (2012)

Michaela Fakiola:

UWA Raine Visiting Fellowship

Richard W Francis:

Winner - TICHHR student symposium presentation prize

Winner - Mike Schon-Hegrad Incentive award for innovation in Information Technology

Joint Winner - Mike Schon-Hegrad Incentive award for innovation in Information Technology

Runner up - Dr Louisa Alessandri Memorial Fund's Publication Prize

Runner up - BUPA Population Health Postgraduate Society Postgraduate Research Symposium Presentation prize

Highly Commended - Dr Louisa Alessandri Memorial Fund's Excellence and Commitment to Research award (peer nominated)

Genevieve Syn:

Travel Award Friends of the Institute of Child

Heath Research (2012)

## External Committees

### INTERNATIONAL

Jenefer Blackwell:

Wellcome Trust Case Control Consortium 2 – Management Committee

Wellcome Trust Case Control Consortium 2 – Publications Committee

Gordon Research Conference on Tropical Medicine – Program Committee

### NATIONAL

Jenefer Blackwell:

NHMRC Fellowships Panel (2013)

Editorial Board Genomic Medicine: 2005+

Editorial Board Genes and Immunity: 2006+

### LOCAL

Sarra E. Jamieson:

Princess Margaret Hospital for Children Ethics Committee (NHMRC Recognised)

External advisory panel Aboriginal Health and Medical Research Council

WA State Representative: Australian Epigenetics Alliance

Western Australian DNA Bank Management Committee

Treasurer: Perth Epidemiology Group

## INVITED PRESENTATIONS

Jenefer Blackwell - Fourth meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Co-convenor and Speaker, 8-10 February 2012, Varanasi, India.

Jenefer Blackwell - Meeting of Brazilian Tropical Medicine Research Centre (Leader E. Carvalho, meeting organizer S. Jernomino). Invited Speaker, 28 February to 2 March 2012, Natal and Pipa, Brazil.

Jenefer Blackwell - 2012 Conference From Genomes to Vaccine Development Research, Invited Speaker, 25-28 October 2012, Khon Kaen, Thailand.

Jenefer Blackwell - Fifth meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Co-convenor and Speaker, 30 January to 2 February 2013, Varanasi, India.

Jenefer Blackwell - Gordon Research Conference on Tropical Medicine, Invited Speaker, 10-15 February 2013, Galveston Texas, USA.

Jenefer Blackwell - Meeting of Brazilian Tropical Medicine Research Centre (Leader E. Carvalho). Invited Speaker, 21 to 28 February 2013, Salvador, Brazil.

Saskia Decuypere - Metabolomics-driven development of diagnostics for infectious diseases, invited seminar at Medical Research Council Unit, Fajara (The Gambia), 18 December 2012.

Saskia Decuypere - Metabolomics in Infectious Disease Research, conference 'From Genomics to Vaccine Developmental Research', Khon Kaen

(Thailand), 25 October 2012.

Saskia Decuypere - Metabolomics based biomarker discovery for melioidosis, invited seminar at the Institute of Tropical Medicine, Antwerp (Belgium), 24 May 2012.

Saskia Decuypere - Metabolomics based biomarker discovery for melioidosis and sepsis, invited at Metabolomics Australia, Melbourne node, Bio21 Institute, Melbourne University, Melbourne, 15 May 2012.

Saskia Decuypere - From Cambridge to Australia: new frontiers in looking at infections, invited seminar at the Menzies School of Health Research, Darwin, 20 March 2012.

Sarra Jamieson - Genome-wide association study of recurrent and chronic otitis media. Ear Sciences Institute of Australia Symposium - A Life Worth Hearing. Perth, Australia. June 2012

## ACTIVE collaborations

Mr Andrew Barker, Paediatric Surgeon and Urologist, Hollywood Medical Centre, WA

Mr Mahmoud Bhutta, University of Oxford, UK

Prof Steve Brown, MRC Harwell, UK

Prof Edgar Carvalho and Dr Léa Castellucci, Serviço de Imunologia, Hospital Universitário Prof. Edgard Santos, Salvador, Brazil

Prof Heather Cordell, Professor of Statistical Genetics, Institute of Genetic Medicine, Newcastle University, UK

Dr Michaela Fakiola, Research Associate, Cambridge Institute for Medical Research, University of Cambridge, UK

Prof Ricardo Gazzinelli, Division of Infectious Disease and Immunology, University of Massachusetts Medical School, Massachusetts, USA; Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Brazil; and Centro de Pesquisas René Rachou, CPqRR – Fundação Oswaldo Cruz, Belo Horizonte, Brazil.

Prof Steve Graham, Centre for International Child Health, Melbourne University

A/Prof Tinto Halidou, Clinical Research Unit Nanoro, Burkina Faso

Prof Andrew Holland, Paediatric Surgeon, Children's Hospital Westmead, University of Sydney, NSW

Prof Jan Jacobs, Department of Clinical Sciences, Institute of Tropical Medicine Antwerp, Belgium

Prof Selma Jeronimo, Department of Biochemistry, Universidade Federal do Rio Grande do Norte, Natal, Brazil

A/Prof Lea-Ann Kirkham, University of Western Australia, WA

Prof Sunee Korbsrisate, Mahidol University, Bangkok, Thailand

A/Prof Ganajana Lertmemongkolchai, Khon Kaen University, Thailand

Dr Natasha Nassar, Kolling Institute of Medical Research, The University of Sydney, NSW

Mr Naeem Samnakay, Neonatal and Paediatric Surgeon, Princess Margaret Hospital and Hollywood Medical Centre, WA

Prof Shyam Sundar, Institute of Medical Sciences, Banarus Hindu University, Varanasi, India

Prof Mary Wilson, Department of Internal Medicine, University of Iowa, USA

# INFLAMMATION

## Overview

Sunlight is one of the most important environmental agents to which man is exposed. The ultraviolet B (UVB) wavelengths are the most powerful and cause not only skin cancers, but also suppression of immune responses to antigens introduced at distant body sites. We have previously shown that UVB light administered to the shaved dorsal skin of mice can suppress models of allergic airways disease. This suggested that UV-induced changes in the skin could signal downstream systemic responses to allergens in respiratory tissues. In 2012, we further focussed on the effects of UV irradiation of skin on dendritic cell precursors in the bone marrow. This was important as the bone marrow produces haematopoietic cells that replace those that are dying in the peripheral organs. Erythematous UVB irradiation of skin stimulated the production from bone marrow of poorly functioning dendritic cells. Further, UV-induced prostanoids were responsible for the effects of UV irradiation of skin on dendritic cell precursors in the bone marrow. This result suggested that UV-induced inflammation per se was responsible for this effect and that it was a homeostatic response that ensured that the inflammation in the skin was restricted and did not progress out of control. We have also tested these bone marrow cells in controlling models of established inflammation. The dendritic cells generated from the bone marrow of UV-irradiated mice actively suppressed ongoing responses in antigen-sensitised mice and suggested that the dendritic cells were not only poor in function but actively regulatory. In 2012, we established large numbers of chimeric mice, i.e. mice engrafted

with bone marrow cells from UV-irradiated mice or mice implanted for 3 days with pellets releasing the prostanoid, prostaglandin E<sub>2</sub>. In these chimeric mice, immune responses initiated by dendritic cells were minimal.

In parallel studies we have investigated the effects of UV-induced vitamin D<sub>3</sub> in control of immune cell activity and asthma and obesity models in mice. Humans obtain 90% of their vitamin D<sub>3</sub> from UV irradiation of skin so it has been proposed by us, and others, that UV-induced Vitamin D<sub>3</sub> may contribute to the immunomodulatory effects of UV. We have examined the effect of vitamin D<sub>3</sub> in excess (painted onto the skin of mice with normal levels of vitamin D<sub>3</sub>) and in deficiency (mice were fed diets restricted in vitamin D<sub>3</sub>). We discovered that male vitamin D<sub>3</sub>-deficient mice were unable to respond to UVB irradiation of skin for vitamin D<sub>3</sub> production. Thus, if the male mice responded to UVB for regulation of immunity, this was not via the modulatory properties of vitamin D<sub>3</sub>. This finding has given us an exciting and ongoing approach to analyse the relative contribution of vitamin D<sub>3</sub> and other UV-induced mediators to the immunomodulatory properties of UV irradiation. We have also shown that vitamin D<sub>3</sub>-deficient mice express worse symptoms of asthma. We have shown that vitamin D<sub>3</sub> and UV irradiation of skin have different effects on reducing the symptoms associated with obesity.

In 2012, our studies of the mechanism of action of interleukin-4 as an anti-inflammatory cytokine for human monocytes and macrophages continued. Gene arrays gave new candidate molecules that may be involved in the mechanism by which IL-4 suppresses inflammatory mediator production.

In June 2012, Dr Jason Waithman joined the Inflammation Division. Dr Waithman is an NHMRC Early Career Research Fellow from the Ludwig Institute in Melbourne. He has an international reputation in dendritic cell research following his training at some of the best immunology laboratories in Melbourne. Dr Waithman has initiated several murine models of melanoma at TICHR and is studying the recognition of melanoma antigens by different immune cells. He has established sophisticated immune models by which antigens are cloned into the melanoma cells and their recognition by cells of transgenic mice under- or over-expressing receptors for that antigen analysed.

## EFFECT OF UV IRRADIATION OF SKIN ON DENDRITIC CELLS GENERATED BY CULTURE FROM THE BONE MARROW

NM SCOTT, RLX NG, PH HART

We have previously shown that signals sent from skin irradiated with erythematous UV to the bone marrow stimulate the development of dendritic cells that are poorly immunogenic and cannot induce a strong immune response. The phenotype and function of cells generated by culture from the bone marrow of animals administered a single inflammatory dose of UV, or multiple lower doses of UV radiation, have been studied. Different growth factors have been added to the cells in culture to generate these poorly immunogenic dendritic cells. Both GM-CSF and FMS-related tyrosine kinase 3 (Flt3-L) have been used and represent inflammatory and steady-state conditions, respectively, and stimulate different progenitor populations to differentiate. As poorly immunogenic dendritic cells are generated under all differentiative

conditions, we speculate that early progenitors are altered by UV irradiation of skin. The dendritic cells generated in culture have also been able to actively down-regulate immune responses in mice already sensitised and responding to antigen. Thus, the bone marrow-derived dendritic cells from UV-irradiated mice are regulatory dendritic cells.

*Funded by NHMRC, UWA Postgraduate Award to RLXN, Perron award to RLXN.*

## EFFECT OF UVB AND PROSTAGLANDIN E<sub>2</sub> ON BONE MARROW CELLS ENGRAFTED INTO CHIMERIC MICE

RLX NG, NM SCOTT, S GORMAN, PH HART.

Regulatory dendritic cells are generated by culture of bone marrow from UV-irradiated mice and results suggest the induction of regulatory cells. To remove the potential artificial effect of bone marrow cell culture, in 2012 we have established several types of chimeric mice. Mice are gamma-irradiated to destroy their bone marrow cells and then injected with bone marrow cells from (a) non-irradiated or UV-irradiated mice, or (b) mice implanted with placebo pellets or pellets releasing prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). The re-establishment of their bone marrow was followed and by 8 weeks, the peripheral lymph nodes had been re-populated. After 16 weeks, the efficiency of the engrafted dendritic cells has been sought as we wish to know whether the effects of the UV or PGE<sub>2</sub> exposure are long-lived. When an inflammatory antigen is painted on the skin of the chimeric mice, there is an inflammatory response in mice engrafted with bone marrow cells from non-

irradiated or placebo-pellet-inserted mice but a very poor response if the mice were engrafted with bone marrow cells from UV-irradiated, or PGE<sub>2</sub>-pellet-inserted mice. This result suggests a long lasting effect of UV irradiation, and by PGE<sub>2</sub> per se, on dendritic cells in the bone marrow.

*Funded by NHMRC, UWA Postgraduate Award to RLXN, Perron award to RLXN.*

## EFFECT OF EXPERIMENTAL ALLERGIC AIRWAYS DISEASE ON BONE MARROW-DERIVED DENDRITIC CELLS

NM SCOTT, RLX NG, S GORMAN, PH HART.

In response to UV-induced inflammation of the skin, bone marrow-derived dendritic cells are regulatory. To determine whether the effect is unique to skin inflammation, the effect of inflammation at other tissue sites has been examined. In response to inflammation in the airways and in the peritoneal cavity (due to administration of the inflammasome activator, alum), bone marrow derived dendritic cells are regulatory. Further their development is blocked by the administration of indomethacin and again suggests that inflammation-induced PGE<sub>2</sub> is responsible. In 2012, chimeric mice were established with bone marrow cells from mice with experimental allergic airways disease. When the chimeric mice had been engrafted for 16 weeks, the response to sensitisation and challenge with respiratory antigens was significantly reduced. When chimeric mice engrafted with bone marrow cells from mice with experimental allergic airways disease were challenged with LPS, the dendritic cells of the airways (previously labelled with a dye) were unable to migrate to the nodes and

stimulate an immune response. We propose that the formation of regulatory dendritic cells in the bone marrow is part of a homeostatic mechanism to limit the destructive properties of respiratory inflammation.

*Funded by NHMRC, UWA Postgraduate Award to RLXN, Perron award to RLXN*

## MECHANISMS OF REGULATION BY IL-4 FOR REDUCED INFLAMMATORY MEDIATOR PRODUCTION BY HUMAN MONOCYTES

EA WOODWARD, PH HART.

We have been studying the mechanisms by which interleukin-4 (IL-4) can suppress inflammatory cytokine production by activated human monocytes and macrophages. Using gene arrays, we continue to search for molecules that may be involved in the anti-inflammatory properties of IL-4. Candidate molecules studied in 2010 include RP-105 (CD180), IL-10, RIPK2 and the transcription factor c-Maf.

*Funded by Murdoch University Students stipend, Perron award to EAW*

## EFFECT OF DIETS DEFICIENT IN VITAMIN D ON ASTHMA SEVERITY

S GORMAN, C WEEDEN, NM SCOTT, RE FONG, DANNY MOK, GRAEME ZOSKY, PH HART

To study the effects of early life vitamin D deficiency, we have established colonies of BALB/c mice fed a vitamin D restricted diet. The effects of gestational and neonatal vitamin D deficiency are examined by feeding female mice and their offspring a vitamin D null diet. The ovalbumin-driven model of allergic airways

disease has been established in these mice. Detailed studies suggest that the models of disease are worse in the vitamin D-deficient mice supporting the hypothesis that vitamin D has a regulatory role in systemic immune diseases such as asthma. Effects of vitamin D deficiency have been measured in both the lymph nodes and the lungs and airways. The effects of vitamin D were more important in male mice and when lower concentrations of allergen were used to develop the model. Our results indicate that vitamin D controls asthma-inducing inflammatory cells in the lungs in a gender-specific fashion through the regulation of respiratory bacteria. The effects of early life vitamin D deficiency were reversed by vitamin D supplementation through the diet. Further studies are in progress to determine on the effects of vitamin D deficiency on various immune cell types, including regulatory T cell and B cells.

*Funded by the Brightspark Foundation*

## STUDIES ON THE IMMUNOMODULATORY EFFECTS OF UV-INDUCED VITAMIN D

S GORMAN, C WEEDEN, NM SCOTT, JL BISLEY, PH HART

To examine whether UV-induced vitamin D is responsible for the immunosuppressive effects of UV, we have taken advantage of our observation that when vitamin D-deficient mice are UVB irradiated, only the female mice are able to respond to increase systemic vitamin D levels. We have developed a powerful model to determine which immunoregulatory responses measured following UV irradiation of skin are

vitamin D-dependent. Indeed, our studies have shown using assays of both systemic and local contact hypersensitivity, and ovalbumin-induced asthma, immunity is suppressed in male and female mice to a similar extent. We have not detected responses to UV in male vitamin D-deficient mice that are vitamin D-dependent. We investigated skin levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, and found that they were increased in female but not male mice after UVR. We have also characterised that skin levels of the vitamin D precursor 7-dehydrocholesterol are significantly reduced in male relative to female mice. These studies are now published in PLoS ONE (doi:10.1371/journal.pone.0046006).

*Funded by the Brightspark Foundation and National Health and Medical Research Council*

## EFFECTS OF UVR AND VITAMIN D ON THE DEVELOPMENT OF OBESITY AND METABOLIC SYNDROME

S GELDENHUYS, PH HART, S GORMAN

Sun exposure has risks and benefits for human health. In Australia, the risks are well appreciated and more recent attention has focused on possible benefits of controlled sunlight exposure, largely considered to be solely through vitamin D. Insufficiency in vitamin D is linked to increased risk of a wide range of diseases, including obesity, the metabolic syndrome (MetS) and type-2 diabetes but the direction of this association is not clear. The prevalence of obesity in Australia and elsewhere has increased over the past 30 years, influenced by lower levels of physical activity and increased consumption of energy-dense

food and drink. Sun exposure has decreased in the last 30 years, as a consequence of lifestyle changes and the success of sun protection messages. In this project we use a murine model of diet-induced obesity to consider whether low dose sun exposure could affect the development of obesity and MetS. This is the Honours project of Ms Sian Geldenhuys. Sian's preliminary data indicates that low dose (sub-erythral) UV irradiation of the skin attenuates the development of obesity and measures of MetS in mice fed a high fat diet. In this project we also seek to determine the vitamin D-dependent and -independent effects of UV on the development of obesity and MetS, and have used the model described above using male vitamin D-deficient mice. As previously observed in BALB/c male mice, C57Bl/6 male mice were unable to respond to UVR to increase their serum levels of 25(OH)D. These studies point to a vitamin D-independent effect of UV for curbing the development of obesity and MetS. In ongoing studies, we are investigating possible mechanistic pathways involving immune cells like regulatory T cells that may be responsible for abating MetS development in UV-irradiated mice.

*Funded by the Brightspark Foundation*

## MECHANISMS BY WHICH VITAMIN D SUPPRESSES SKIN INFLAMMATION

S GORMAN, PH HART

Active vitamin D analogues are currently used in the clinic to treat inflammatory skin conditions like psoriasis. We have previously shown that vitamin D applied to the skin (topically) increases the ability of immune cells like regulatory T

cells to suppress subsequent skin-induced inflammation. The increased suppressive ability of the regulatory T cells was induced by skin-derived dendritic cells, and required the expression of the cytokine, interleukin-2. In 2012, we investigated how topically-applied vitamin D suppressed the development of mast cell-mediated immune responses, using the contact sensitiser, di-nitrofluorobenzene to induce a biphasic hypersensitivity reaction in the ear skin of mice. Topically-applied vitamin D suppressed the T cell-dependent phase (effluent) of this reaction, when applied immediately or up to 6 days before the contact sensitiser. Our preliminary investigations have linked this observation with enhanced mast cell numbers in the skin and reduced mast cell numbers in the skin-draining lymph nodes of vitamin D-treated mice. In ongoing studies, we will investigate the links between increased activity of regulatory T cells and mast cells in the skin following topical vitamin D. These studies highlight how skin treatment with active vitamin D analogues may be a useful treatment for the suppression of allergic or inflammatory responses, which are initiated in the skin.

*Funded by the Brightspark Foundation*

## Shelley and Jasons projects to add

### Staff and Students

#### RESEARCH STAFF

Prue H Hart BSc (Hons) MSc PhD, NHMRC Principal Research Fellow

Jason Waithman BSc (Hons) PhD

Shelley Gorman BSc (Hons) PhD

Naomi M Scott BSc (Hons), PhD awarded U of Newcastle 2012

Ben Wylie BSc (Hons)

#### POSTGRADUATE STUDENTS

Eleanor A Woodward BSc (Hons), PhD awarded March 2012

Royce LX Ng BSc (Hons), PhD Candidate

#### THESES PASSED

Eleanor Woodward, PhD March 2012

### Awards

Prue Hart, Adjunct Professor, University of WA, NHMRC Principal Research Fellowship

Shelley Gorman, Brightspark Research Fellowship 2011-2013.

Jason Waithman, NHMRC Biomedical Training Fellowship

Jason Waithman, Cancer Australia and Cure Cancer Australia (2 grants)

Jason Waithman, Institute Small Grant, Telethon Institute for Child Health Research

### Invited Presentations

Prue Hart, ASCIA WA conference, Perth Zoo, Perth WA, July

Prue Hart, Departmental seminar, Microbiology, UWA, August

Prue Hart, Poster Presentation, DC2012, Daegu, Korea, October

Prue Hart, UWA Population Health Postgraduate Society, Perth. November

Prue Hart, MEPSA/AHMRC, Adelaide. November

Prue Hart, Inflammation Conference, Melbourne. November

Prue Hart, Australasian Society for Immunology, Melbourne. December

Jason Waithman, Australasian Society of Immunology Annual Conference—Tumour Immunology Workshop (2012)

Jason Waithman, Inaugural National Melanoma Conference (2012: Australia)

Jason Waithman, Combined Biological Sciences Meeting (2012: Australia)

Jason Waithman, National Centre for Asbestos and Related Diseases (2012: Australia)

Jason Waithman, Tumour Immunology Group, Sir Charles Gardner Hospital (2012: Australia)

Jason Waithman, Dept of Microbiology and Immunology, The University of Melbourne (2012: Australia)

Shelley Gorman, Sydney Medical School, University of Sydney (Sydney, May 2012).

Shelley Gorman, The 23rd Combined Biological Sciences Meeting (Perth, August 2012).

Shelley Gorman, Edith Cowan University, School of Medical Sciences (Perth, September 2012).

Shelley Gorman, The Australian Health and Medical Research Congress (Adelaide, November 2012).

Royce Ng, Journal Club presentation (for combined meeting with Cell Biology) March

Royce Ng, Data presentation (for combined meeting with Cell Biology) April

Royce Ng, Private data presentation for Professor Warren Alexander (Telethon Institute) May

Royce Ng, Data presentation (for combined meeting with Cell Biology) July

Royce Ng, Private data presentation for Professor John McGrath (Telethon Institute) August

Royce Ng, Data presentation for Telethon Institute Research Seminar Series. September

Royce Ng, Poster Presentation at the International Symposium for Dendritic cells (Daegu, South Korea) October

Royce Ng, Private data presentation for laboratory of Professor Paul Kubes (Calgary, Canada) October

Royce Ng, Private data presentation for laboratory of Professor Margaret Goodell (Houston, USA) October

Royce Ng, Oral and Poster presentation at The Australian Health and Medical Research Congress (for MEPSA, Adelaide Convention Centre). November

## External Committees.

Prue Hart, Invited Member, NHMRC Academy

Prue Hart, Sole External Member, Royal Perth Hospital Medical Research Foundation Scientific Committee.

Prue Hart, President (till May), Australasian Society for Dermatology Research. From May 2012, immediate Past President

Prue Hart, Member, Organising Committee, Australasian Society for Dermatology Research Annual conference, Sydney, May 2012.

Shelley Gorman, Molecular and Experimental Pathology Society of Australia (Secretary)

## ACTIVE collaborations

Dr Michele Grimaldeston, Centre for Cancer Biology, Adelaide

A/Professor Vance Matthews, West Australian Institute for Medical Research

A/Professor Prue Cormie, Edith Cowan University, Western Australia

A/Professor Robyn Lucas, Australian National University, Canberra ACT

# LUNG GROWTH AND RESPIRATORY ENVIRONMENTAL HEALTH

## Overview

We have three major research themes 1) early life determinants of lung growth, 2) respiratory environmental health and 3) mechanisms of airway dysfunction in asthma. These research themes overlap in several areas and underpin our overall goal to understand the early life factors that contribute to respiratory disease. These factors include environmental exposures, viral infection, allergic sensitization, nutritional deficiencies and genetic variability in innate lung function responses. It is becoming increasingly clear that early life exposures make a substantial contribution to respiratory morbidity and by understanding key lung development processes we aim to design interventions that will ultimately prevent the onset of respiratory disease and improve lung health in the community.

This research relies heavily on mouse models and the state of the art techniques for assessing lung function and structure that have been developed in our laboratory through ongoing collaborations with Prof Zoltan Hantos (University of Szeged, Hungary) and Prof Peter Sly (University of Queensland). These studies involve a multi-disciplinary approach whereby epidemiological and clinical studies inform the design of mechanistic animal studies; which are in turn used to identify issues that require further investigation in terms of clinical outcomes and public health. This approach is facilitated through collaborations with researchers examining clinical outcomes (Collaborators: A/Prof Graham Hall, TICHR; Prof Steve Stick, PMH; Prof Peter Sly, UQ) and environmental exposure studies (Collaborators: A/Prof Merci Kusel, TICHR; A/Prof Angus Cook,

U.W.A; Dr Andrea Hinwood, ECU; A/Prof Ben Mullins, Curtin). We also combine our measures of lung function with structural (stereology and *in vivo* imaging) and genetic studies (Collaborators: Dr Anthony Bosco, TICHR; Dr Kim Carter, TICHR) with a view to understanding critical pathways involved in lung growth and development and how these may be altered by early life insults resulting in a predisposition for disease. These studies on early life factors that impact on lung growth and disease are complemented by our ongoing work examining the mechanisms of airway hyperresponsiveness in obstructive disease. These studies are largely driven by Dr Peter Noble's *in vitro* and *in vivo* (human/animal model) work which tests new concepts of airway smooth muscle physiology and how these impact airway function in health and disease (Collaborators: A/Prof Alan James, SCGH; Prof Howard Mitchell, UWA; Dr Peter McFawn, UWA; Prof David Sampson, UWA; A/Prof Robert McLaughlin, UWA).

This work is further facilitated by our longstanding collaboration with A/Prof Andreas Fouras (Monash) where we have been developing the next generation of lung imaging technology which is likely to revolutionise our understanding of lung structure and function.

## Early life determinants of lung growth

### VITAMIN D DEFICIENCY AND LUNG GROWTH

RACHEL FOONG, SHELLEY GORMAN, PRUE HART, TIM LECRAS (CINCINNATI) GRAEME ZOSKY

There has been a dramatic increase in recent decades in the prevalence of vitamin D deficiency in Australia and worldwide. Vitamin D deficiency is associated with a number of diseases including, 1) the bone disorder rickets (due to the importance of vitamin D in calcium homeostasis), 2) autoimmune disorders and 3) cardiovascular disease. Recent prominent publications have also implicated vitamin D in the pathogenesis of obstructive lung diseases such as asthma and COPD. Additionally, epidemiological studies have shown a strong association between serum vitamin D levels and lung function suggesting an important link between vitamin D status and lung health. However, there had been no study showing a direct link between vitamin D deficiency and lung growth/structure/function. In 2010 we published a study in the leading respiratory journal (American Journal of Respiratory and Critical Care Medicine) on the lung structure and function of mice raised on vitamin D deficient and replete diets. We showed for the first time that vitamin D deficiency alters lung structure resulting in significant deficits in lung function. This study received considerable public interest resulting in an international media release by the American Thoracic Society and interviews for ABC Radio National. These studies are ongoing and we now plan to identify the mechanism of vitamin D deficiency induced alterations in lung growth. This work is being pursued by Rachel Foong who began a PhD in 2011 examining the role of vitamin D deficiency airway remodelling in chronic lung disease. Rachel has shown that vitamin D deficiency alters the structure of the airway such that it is more prone to constrict. This is a central feature of many chronic lung diseases and may explain the link between

vitamin D deficiency and chronic lung diseases.

Funding: NHMRC Project Grant (2013-2015).

## Respiratory environmental health

### ARSENIC INDUCED NON-MALIGNANT LUNG DISEASE

KATHRYN RAMSEY, PETER SLY (UQ), ALEXANDER LARCOMBE, GRAEME ZOSKY

The contamination of groundwater with arsenic (As) is a global health problem and it is estimated that 100's of millions of people around the world are exposed to unsafe levels of arsenic in their drinking water. Arsenic is a well recognised carcinogen and is listed by the International Agency for Research on Cancer (IARC) as a category 1 carcinogen. However, recent evidence from an exposure event in Chile has suggested that As is linked to the development of non-malignant obstructive lung disease. In particular, *in utero* exposure to As via drinking water has been linked to increased mortality due to bronchiectasis in young adults.

In order to investigate the link between early life As exposure and the development of lung disease in later life we conducted a series of experiments using mouse models of *in utero* As exposure. We began pilot studies in 2008 which involved exposing pregnant mice from three strains (C57BL/6, C3H/HeARC, BALB/c) to 100 ppb (or 0 ppb as a control) via their drinking water from gestational day 8 (prior to the development of the lung buds at day 9.5) until birth. The offspring of these mice had their lung function measured at 2 weeks of age. We found that there was no difference in lung



mechanics corrected for lung volume in BALB/c mice exposed to As compared to controls. In contrast C3H/HeARC mice exposed to As had significantly higher airway resistance for a given lung volume compared to controls and As exposed C57BL/6 had higher tissue damping and elastance for a given lung volume compared to controls. These experiments provided the proof of concept data required to demonstrate the potential of As to alter lung development which may explain the link between early life arsenic exposure and poor lung health in later life. We have since completed an indepth genetic analysis of lung tissue samples from these mice and found that genes related to lung branching and mucous clearance were altered by arsenic exposure. These are important findings as they provide, for the first time, a direct mechanism that may explain the association between lung disease and arsenic exposure via drinking water observed in human populations. This work was published in 2012 in the leading Environmental Health Journal (Environmental Health Perspectives).

In 2012 we also completed a series of studies examine the effect of combining arsenic exposure with an additional respiratory insult using a mouse model of influenza infection. These data clearly demonstrate that arsenic can exacerbate influenza induced inflammation and alterations in lung function. These respiratory deficits also persisted into adulthood demonstrating the importance of early life environmental and viral exposures in determining adult lung health. Together this work forms the basis of Kathryn Ramsey's PhD which is due for submission in 2013.

*Funding: NHMRC Project Grant (2010-2012)*

## REGIONAL ENVIRONMENTAL DETERMINANTS OF LUNG HEALTH

GRAEME ZOSKY, RUSSELL WONG, ROBERT WOODWARD (U.W.A.), LUCIA GUITERREZ (U.W.A.), BRIAN DEVINE (U.W.A.), FIONA MALEY (U.W.A.), ANGUS COOK (U.W.A.)

Exposure to high levels of geogenic (earth derived) dust in regional towns in Australia is a public health concern. In particular, children have been identified as a subgroup that is at high risk of respiratory disease as they are active close to the ground, have higher ventilation rates than adults and often play in areas (e.g. community playgrounds and outdoors) where dust levels are high. This study is the first to directly assess lung responses to inhaled "real world" particles from remote and regional towns in Australia.

In 2010 we completed Phase 1 of the *in vivo* animal exposure studies associated with this project. In these studies adult BALB/c mice were exposed to varying (0, 10, 30, 100 µg) concentrations of PM<sub>10</sub> (< 10 µm) collected from Newman and Kalgoorlie suspended in 50 µL of saline by intranasal inoculation under light anaesthesia. Mice were assessed for inflammatory responses in the lung 6, 12, 24 hrs and 7 days post inoculation. The magnitude of the influx of inflammatory cells was dependent on the dose and sample used. A significant influx of neutrophils was observed in the mice exposed to PM<sub>10</sub> from both Kalgoorlie and Newman with a greater response in mice exposed to PM<sub>10</sub> from the latter. In 2012 we completed Phase 2 of these studies using samples collected from across W.A. (Kalgoorlie, Tom Price, Newman, Karratha, Port Hedland) with a view to identifying the key components of the dust

that have the biggest impact on lung outcomes. We are currently analyzing the large data set associated with these studies and have some exciting insights into the key drivers of the lung response to inhaled dust.

In 2012 we extended this study to examine the interaction between exposure to geogenic dusts in influenza infection. While this study is ongoing our preliminary analysis suggests that exposure to dust *significantly* enhances the response to influenza infection.

*Funding: CRC for Asthma, Thoracic Society of Australia and New Zealand*

## ENVIRONMENTAL HEALTH OF REMOTE INDIGENOUS COMMUNITIES

HOLLY CLIFFORD, GRAEME ZOSKY, ROZ WALKER, GLENN PEARSON

There is a significant gap in health between indigenous and non-indigenous Australians. This is particularly true for respiratory health and in individual living in remote communities. In 2011 we commenced a research program designed to assess the role of the environment, with a focus on water quality and dust exposure, in contributing to this disparity in respiratory health. We travelled to several communities of the Martu people in the eastern Pilbara and collected water and dust samples for analysis of heavy metal contamination. We are now expanding this program to conduct real-time monitoring of the inhalable dust with a view to estimating exposure levels in the community.

*Funding: Thoracic Society of Australia and New Zealand*

## DIESEL EXHAUST EXPOSURE AND ITS EFFECTS ON LUNG FUNCTION AND EXACERBATIONS OF AIRWAYS DISEASE

ALEXANDER LARCOMBE, BEN MULLINS (CURTIN), RACHEL FOONG, GRAEME ZOSKY

This ongoing project is designed to investigate the mechanisms behind air pollution (specifically diesel exhaust and woodsmoke) induced exacerbation of airways disease. In 2009 and 2010 we established a mouse model of acute diesel exhaust particle (DEP) exposure using intra-nasal instillation of DEP (ie small amounts of DEP in solution are placed on the nose of mice and inhaled). At a variety of time-points post exposure (ranging from 3 hours to 4 weeks) we took bronchoalveolar lavage fluid for assessment of inflammation and uptake of carbon black by alveolar macrophages. We identified significant cellular inflammation which peaked ~6 hours post exposure. We also measured increased levels of a number of cytokines including MIP-2 and MCP-1 post exposure. Cellular inflammation had largely resolved 48 hours post exposure. We also measured lung volume, baseline lung function and lung mechanics over 20cm H<sub>2</sub>O inflation/deflation manoeuvres for these mice 6 and 24 hours post exposure. We noted impaired lung function at 6 hours, which had returned to normal after 24 hours. A significant component of this project was assessing uptake of DEP by alveolar macrophages. We measured a distinct bi-phasic uptake of DEP at levels comparable to those seen in children chronically exposed to soot / DEP, indicating the real-world relevance of these studies.

In 2011 and 2012 we combined this DEP model with our established model of influenza infection

and clearly demonstrated that DEP can enhance viral replication and exacerbate influenza induced inflammation. This observation has the potential to influence how people who are hospitalized with influenza are treated and to inform public health warnings on high pollution days.

In 2011 and 2012 we established a mouse model of whole diesel exhaust exposure by exposing mice to exhaust generated by a Euro 1 diesel engine under partial load. Exhaust gases and particles were assessed prior to entering an exposure chamber containing mice. Engine load was adjusted to obtain particle concentrations of 20 or 30mg/m<sup>3</sup>. Mice were exposed for 2 hours per day for 8 days. During exposure, oxygen levels remained at ~20% and levels of other exhaust gases remained within short term human exposure guidelines. Exposure resulted in a dose dependent inflammatory response with the greatest pulmonary inflammation and impairment in lung function occurring 24 hours after exposure to 50mg/m<sup>3</sup>.

## BIODIESEL EXHAUST EXPOSURE AND RESPIRATORY HEALTH

ALEXANDER LARCOMBE, BEN MULLINS (CURTIN), ANTHONY KICIC (PMH)

Biodiesel is a renewable fuel made from a variety of plant or animal oils. It is often seen as a “green” or healthier alternative to finite sources of mineral diesel, however, recent studies show that biodiesel exhaust has certain physical and chemical characteristics that also make it dangerous to health. This ongoing study employs a range of *in vitro* and *in vivo* exposure studies, detailed physical and

chemical assessment of exhaust characteristics and gene expression profiling to identify what characteristics make a “healthy” or “unhealthy” biodiesel and understand the mechanisms of biodiesel exhaust induced disease.

In 2012 we made and combusted our own canola biodiesel, and measured a range of physico-chemical properties of the exhaust. We found that canola biodiesel combustion produced a greater number of particles <1µm in diameter and particles with a higher surface area to volume ratio compared to mineral diesel particles. We also showed that canola biodiesel exhaust contained greater amounts of oxides of nitrogen, carbon monoxide, carbon dioxide and oxides of sulfur compared to mineral diesel.

In 2012 we also exposed human airway epithelial cell cultures to diluted exhaust generated by combusting mineral diesel, 100% canola biodiesel, 20% canola biodiesel or pure canola oil in an unmodified diesel engine under partial load. We assessed cell viability and apoptosis 24 hrs after exposure, and inflammation (IL-6, IL-8 and RANTES) 6, 12 and 24 hours after exposure. We found that, even using the same renewable oil type (canola) there were significant differences in response to different blends. In general, exposure to exhaust from B100 or B20 combustion resulted in greater inflammation and reduced viability compared to exposure to mineral diesel exhaust. Apoptosis was highest in cells exposed to mineral diesel exhaust.

## Mechanisms of airway hyperresponsiveness in asthma

## NOVEL IMAGING MODALITIES FOR THE ASSESSMENT OF REGIONAL AIRWAY CONTRICTION

GRAEME ZOSKY, ANDREAS FOURAS (MONASH)

In 2011 we established a collaboration with researchers at Monash University who are developing novel methods for imaging the lung using highly coherent synchrotron based radiation. These studies are conducted at the third generation synchrotron in Japan and are yielding novel insights into the regional effects of bronchoconstricting agents. In 2012 we submitted a patent for a novel imaging technology and were able to secure funds through an NHMRC Development Grant to establish this technique in A/Prof Fouras’s lab in Melbourne.

*Funding: NHMRC Development Grant (2013-2015)*

## VIRAL INDUCED AIRWAY HYPERRESPONSIVENESS

ALEXANDER LARCOMBE, JENNIFER PHAN, RACHEL FOONG, ANTHONY KICIC, STEVE STICK, PETER SLY, PETER NOBLE (KEMH), GRAEME ZOSKY

These studies span a number of different projects and involve infecting mice with respiratory viruses (primarily rhinovirus and influenza) at different ages and under different conditions (e.g. in the presence of other respiratory insults). In 2010 and 2011 we focused on 2 aspects; the role of neutrophil elastase in the progression of influenza induced airway hyperresponsiveness (AHR) and the impact of diesel exhaust particle (DEP) exposure during acute influenza infection. In 2011 we published studies on the sexual dimorphism in response

to influenza infection in mice, and in 2012 we published a methodological study on the best technique to assess lung function in mice with influenza induced respiratory disease.

In 2012 we made significant progress in our studies on how rhinovirus infection alters the development of pathogenesis of allergic airways disease. This was prompted by recent studies which show that rhinovirus (HRV) infections account for ~90% of asthma exacerbations, however our understanding of HRV-induced disease is incomplete. A recently developed mouse model of HRV, which we combined with a mouse model of allergic airways disease using house dust mite, allowed us to directly investigate the effects of HRV infection on physiological and immunological respiratory system development. We hypothesized that early life HRV infection impairs physiological and immunological lung growth and development, disrupts antigen presenting cell (APC) function and thus results in exacerbation of allergic airways disease.

In 2012 we completed a series of studies addressing the above hypothesis. We infected mice with HRV in early life (7 days old) and studied the effects of this infection on lung function, and responsiveness to methacholine in adulthood. We also superimposed a mouse model of allergic airways disease (house dust mite) onto HRV infection to assess whether early life HRV infection potentiates asthma development. We hypothesized that HRV infection would exacerbate allergic airways disease in adult mice and that early life infection plus allergic sensitization would enhance airway hyper-responsiveness (AHR) in adulthood. To test these hypotheses, BALB/c mice were

inoculated with house dust mite and/or HRV before measurement of lung function and responsiveness to methacholine. We also assessed viral load, cellular inflammation and serum antibodies. The greatest effects were seen in HDM exposed mice which had altered lung mechanics, AHR and increased inflammation. There were limited effects of HRV alone, however in adult mice, additive effects of HDM and HRV contributed to neutrophilic inflammation and there was an interaction between HDM and HRV in some parameters of lung function. In neonatal mice, more macrophages were seen in mice exposed to both respiratory insults compared with either insult alone. No exacerbation of AHR was seen due to the combination of HDM and HRV.

*Funding: UWA Research Development Award, ARC Discovery Grant, NHMRC Project Grant (2012-2014)*

## EMERGING MODELS OF ASTHMA

ALEXANDER LARCOMBE, GRAEME ZOSKY, PETER NOBLE (KEMH)

Experimental mouse models of aeroallergen sensitization have helped advance our understanding of respiratory diseases such as asthma. Traditional mouse models, however, have a number of inherent draw-backs and are far from the ideal model of human allergic airways disease. Typically, mouse models of “asthma” involve systemic sensitization of adult animals where allergen (usually ovalbumin, from chicken eggs) is used in conjunction with powerful chemicals to enhance the response. Whilst still an extremely valuable tool for the investigation of allergic airways disease

in mice, this situation does not mimic the process in humans, which happens at an early age across the nasal mucosa. To address this, we have designed a project to validate and to further characterize two mouse models of house dust mite (HDM) sensitization and by this assess the impacts of such sensitization/exposure on respiratory health. Mouse models of HDM exposure have strong links to human allergic airways disease and are potentially a considerable improvement on other mouse models. This is because HDM, unlike ovalbumin, is a cosmopolitan guest in human habitation, and naturally causes allergic airways disease in humans. Unlike earlier studies by other researchers, we will use an array of specialised in-house techniques suitable for measurement of lung function in mice, allowing us to reveal important physiological effects of HDM that may have been previously overlooked.

To date, we have conducted two experiments where BALB/c mice were exposed to house dust mite protein. In the first model, we exposed adult BALB/c mice to 25µg HDM protein in saline daily for ten sequential days. In the second model, neonatal BALB/c mice were exposed to low dose HDM (10 to 15µg) 3 times per week for 7 weeks. Control mice received saline only. The mice receive the HDM intranasally, mimicking the route of exposure in humans. We then measured lung volume, baseline lung mechanics and hyperresponsiveness to methacholine 24, 48 and 72 hours post the final exposure. We have shown significant impacts on lung function, including airway hyperresponsiveness for HDM exposed mice. Impacts were greatest 24 hours after the final exposure. We also took blood and bronchoalveolar fluid from these mice for

analysis of total IgE and cellular inflammation. Adult mice showed significantly increased total IgE and eosinophilia, two key features of allergic airways disease. Mice exposed to HDM from early life showed increased HDM specific antibodies, impairment in lung function (including airway hyper-responsiveness) and increased pulmonary inflammation compared to controls. These mice did not exhibit eosinophilia, but instead had a strong neutrophilic inflammation suggesting the neonatal HDM model may not effectively replicate allergic sensitization in humans.

## AIRWAY SMOOTH MUSCLE AS AN INDEPENDENT PREDICTOR OF ASTHMA

PETER NOBLE (KEMH), ALEXANDER LARCOMBE, GRAEME ZOSKY, ALAN JAMES (SCGH), TIMOTHY LECRAS

The primary airway structure/function abnormalities in asthma include increased airway smooth muscle (ASM) mass and exaggerated airway narrowing. Importantly, recent data show that ASM mass is increased early in the natural history of asthma and remains relatively constant throughout life. This argues against the conventional paradigm whereby repeated allergic inflammation drives the remodelling process. We *hypothesise* that the mechanism producing increased ASM in asthma is independent of allergic inflammation and that the combination of increased ASM mass and allergy is required to produce allergic asthma. The **specific aim** of the project is to combine a newly developed mouse model of increased ASM mass with an existing model of allergic airways disease to assess the

relative contributions of ASM mass and allergic inflammation to the asthmatic phenotype.

This NHMRC funded project began in 2012. The first stage of the project was to have the required mouse genotypes re-derived and sent to our Perth laboratory. The mouse models were characterised by our collaborator Professor Timothy Le Cras in his Ohio (USA) based laboratory. The required mouse genotypes have now been successfully re-derived and the mouse colony established at TICH. In 2012 we exposed mice to doxycycline, which upregulates TGFα expression in the airways, producing ASM growth in mice that are KO for Egr-1. We now have preliminary data in KO mice exposed to doxycycline demonstrating greater ASM mass, increased airway narrowing to methacholine challenge and other changes in lung mechanics (e.g. increased baseline resistance).

*Funding: NHMRC Project Grant (2012-2014)*

## Staff and Students

### HEAD OF GROUP

Graeme R Zosky PhD MBIostat

Principal Investigator, Telethon Institute for Child Health Research

Associate Professor, Centre for Child Health Research, The University of Western Australia

### RESEARCH STAFF

Alexander Larcombe PhD

Associate Principal Investigator, Telethon Institute for Child Health Research

Associate Professor, Centre for Child Health Research, The University of Western Australia

Holly Clifford PhD

Lecturer, Centre for Child Health Research, The University of Western Australia

Luke Berry BSc

Kara Perks BSc (Hons)

Thomas Iosifidis BSc (Hons)

Research Assistant Professor Peter Noble PhD (Honorary member)

## POSTGRADUATE STUDENTS

Rachel Foong BSc(Hons) PhD Candidate

Kathryn Ramsey BSc(Hons) PhD Candidate

## HONOURS STUDENTS

Jennifer Phan BSc

Laura Coleman BSc

## RESEARCH SUPPORT

Marina Stubbs

## THESES PASSED

Jennifer Phan BSc (Hons) 1st Class

Laura Coleman BSc (Hons) 1st Class

## Awards

Alexander Larcombe, Health Ledger Career

Development Award

Peter Noble, Asia Pacific Society of Respiratory Travel Award

## External Committees

### INTERNATIONAL

Graeme Zosky. American Thoracic Society Respiratory Structure and Function Planning Sub-Committee

### NATIONAL

Graeme Zosky. (Deputy Chair) Australian Synchrotron Imaging and Medical Beamline Program Advisory Committee

### LOCAL

Graeme Zosky. Thoracic Society of Australia & New Zealand (WA) Executive Committee.

Rachel Foong. Thoracic Society of Australia & New Zealand (WA) Associates Committee.

Alexander Larcombe. University of Western Australia Animal Ethics Committee.

## Invited Presentations

Graeme Zosky. COPD8 UK 2012 "Animal models of vitamin D deficiency"

Graeme Zosky. School of Anatomy, Physiology and Human Biology Seminar Series, U.W.A. "Environmental exposure and the lung"

Alexander Larcombe. 8th International Conference on Air Quality 2012 "Acute Diesel

Exhaust Particle Exposure Increases Viral Titre And Inflammation Associated With Existing Influenza Infection But Does Not Exacerbate Deficits In Lung Function"

## ACTIVE collaborations

Assoc Prof Angus Cook, University of Western Australia

Prof Alan James, Sir Charles Gairdner Hospital, W.A.

Prof Zoltan Hantos, University of Szeged, Hungary

Prof Peter Sly, University of Queensland, QLD

Prof Steve Stick / Dr Anthony Kicic, Princess Margaret Hospital, W.A.

Dr Andrea Hinwood, Edith Cowan University, W.A.

Assoc Prof Andreas Fouras (Monash)

Professor Stuart Hooper (Monash)

Assoc Prof Ben Mullins, Curtin University, W. A.

Dr Alma Fulurija / Prof Barry Marshall, University of Western Australia.

Professor John Mamo, ATN Centre for Metabolic Fitness, Curtin University, W. A.

# MOLECULAR BIOTECHNOLOGY

## Overview

The molecular biotechnology research group has focussed on the use of recombinant protein and protein purification technologies to make valid measurements of immune responses to antigens and allergens and to dissect out interactions and associations that can define the pathogenesis of disease and to develop therapies. One of the two major endeavours for 2012 was to estimate the contribution that different proteins produced by the cat make to the cause of cat allergy and to examine whether immunotherapy with one of allergenic proteins can affect the allergic responses to the others. The results found that people displayed a great deal of heterogeneity in their allergic responses to cats but despite this a trial, where a method of immunotherapy with one allergenic protein was examined, showed regulatory responses were induced to allergens other than the target protein. This result shows that the possibility that the type of immunotherapy trialled would be an excellent candidate to use for other complex sources of allergen such as house dust mites. The second major endeavour has been to use viral capsid proteins as antigens to dissect out quantitative characteristics of immune responses to the different rhinovirus species and to related enterovirus, noting that despite their shared name, rhinovirus A, B and C are distinct and quite disparate species of enterovirus. The antibody responses to the common rhinovirus A were higher in children in children with asthma indicative of more frequent infections while their responses to the gut-tropic ECHO virus were lower. Both findings open new avenues of research with the gut observations pointing to its importance of this

tissue in regulating immunological homeostasis of mucosal tissues.

## ANTIBODY RESPONSES OF ASTHMATIC CHILDREN TO RHINOVIRUS AND OTHER ENTEROVIRUSES

J. IWASAKI, L.A. HAZELL, W. R. THOMAS, B. J. HALES WITH P.N. LESQUEF AND COLLEAGUES SCHOOL OF PAEDIATRICS AND CHILD HEALTH, UWA

Two recombinant VP1 capsid proteins representing two isolates of each of the type A, B and C species of human rhinovirus were made along with VP1 capsid proteins of poliovirus Sabin and ECHO virus. Size exclusion chromatography identified and isolated a molecularly discrete product and circular dichroism showed it had secondary structure consistent with natural VP1. Following documentation of the cross reactivity patterns of antibodies to the different VP1 antigens an absorption strategy was adapted so total antibody titres to each antigen could be measured and then the species-specific titres. The titres to the two isolates of each of rhinovirus species were highly correlated showing they provided a good representation for their respective species. The first major finding was that the VP1 antigens from rhinovirus C bound high titres of antibodies but except for a few people most of this was cross reactive especially with type A while contrarily a high percentage of the titres to type A was not cross reactive to type C. The low type C-specific responses were found in asthmatic and non-asthmatic children, the low response in the latter not being consistent with the simple

notion of more prevalent infections in these subjects. The type A responses however showed markedly increased titres in asthmatic children consistent with more infection. The type B responses in children showed low species-specific titres and no differences in asthmatics although unlike for type C capsid antigen, antibodies specific for type B were readily found in adults. The total antibody titres of asthmatics binding to the Sabin virus were lower in the asthmatics than controls but further study showed this was mostly due to a larger effect from the titres of responses to the related ECHO virus that were markedly lower in asthmatics. This provides evidence that like studies with bacteria that gut viral infections have a close association with the risk of developing asthma. The respective increased and decreased antibody response of asthmatic children to rhinovirus type A and ECHO virus provide new avenues for investigation and possible therapy while the mechanisms that lead to low anti-type C-specific responses in children and adults might underlie the propensity for producing serious respiratory infections.

## IGE AND IGG BINDING TO DIFFERENT CAT ALLERGENS AND CYTOKINE RESPONSE CHANGES WITH ANTIGENIC PEPTIDE IMMUNOTHERAPY

W.A. SMITH L. A. HAZELL, W. R. THOMAS, B. J. HALES WITH PROF M. LARCHE AND COLLEAGUES HAMILTON UNIVERSITY CANADA.

Sera from adult subjects who develop allergic symptoms when exposed to cats were used to examine the binding of IgE, IgG1 and IgG4 antibodies to Fel d 1, Fel d 2, Fel d 3, Fel d

4, Fel d 7 and Fel d 8 allergens as well the undenominated IgE-binding proteins cat haptoglobin and S100A12. It was first noticed that the IgE binding by highly symptomatic subjects could be much lower than that for other allergens such as house dust mite and lower than the arbitrary 0.35 IU/mL used as a diagnostic indicator in allergy practices. The expected importance of Fel d 1 was found but collectively allergens other than Fel d 1 accounted for over 50% of the IgE binding of 40% of the subjects. Although no one allergen approached the binding activity of Fel d 1 an allergen other than Fel d 1 was the highest IgE binding specificity for 35% and an allergen other than Fel d 1 bound more than 50% of the IgE for 25% of allergic subjects. This shows that cat allergy is more heterogeneous than house dust mite allergy where a dominance of a combination of the two major allergens is found for nearly all subjects. From a diagnostic perspective IgE binding titres were greater than 0.35 IU/mL for 79% allergic responders when the binding to all the allergens was summated compared to only 50% if only the anti-Fel d 1 titres were counted. Exhaustive testing of Fel d 3 showed that was not a significant IgE binding specificity and hence not a significant allergen. In collaboration with Professor Larche it was shown that T cells from patients in a clinical trial for immunotherapy with peptides representing Fel d 1 began to make the regulatory cytokine IL-10 not only when activated by Fel d 1 but also when activated by the unrelated Fel d 4 and Fel d 7. It appears that the natural co-exposure of the Fel d 1-treated subjects to the to Fel d 1 and the other cat allergens induced a form of infectious immunoregulation. This is a very desirable for this new type of therapy and shows

it should be applied for other complex allergens. The pattern of IgG antibody showed differences for the type of immune responses elicited by the different allergens. Fel d 1 as documented by others could induce IgG1 and IgG4 antibodies in both cat-allergic and non-allergic subjects. IgG1 was not elicited by other allergens whereas Fel d 4 and Fel d 7 elicited IgG4 antibodies in allergic but not allergic subjects and the other allergens rarely induced any IgG. This heterogeneity suggests a different type of exposure to the allergens or effects from their different biochemical properties.

## Staff and Students

### HEAD OF DIVISION

Wayne R Thomas, PhD BSc (Hons) (Head Division)

Belinda J Hales, PhD BSc (Hons)

Lee Hazell, Dip Appl Sci

### POSTGRADUATE STUDENTS

Jua Iwasaki, BSc (Hons), PhD Candidate

Cibella Gaido, BSc (Hons), PhD Candidate

## Grants

Belinda J Hales, NHMRC project grant, (3 years \$658, 890), Co-investigator. "Investigation into host susceptibility and immune responses in young children with acute wheezing due to human rhinovirus group C infection"

Belinda J Hales, PMH Foundation grant, (1

year, \$79,600) Co-investigator 'Does human rhinovirus species C (HRV-C) suppress adaptive immune responses to respiratory bacteria and other rhinoviruses in asthmatic children?'

## External Committees

W. R. Thomas. IUIS-WHO International Allergen Nomenclature Committee

W. R. Thomas. World Allergy Organization Committee on Aeroallergens

## Internal Committees

Belinda J Hales. Occupational Health and Safety Committee

Belinda J Hales. Telethon Institute Postdoctoral Council

Belinda J Hales. Liquid Nitrogen Committee

Belinda J Hales. Child Health Research Seminar Series co-organiser

## Invited Presentations

W. R. Thomas. Molecular Characterisation of Aeroallergens. Symposium, World allergy organization, World International Scientific Conference, Hyderabad

## Awards and peer recognition

Belinda J Hales. Promoted to Adjunct Associate Professor at the University of Western Australia in 2012

Belinda J Hales. Selected to participate in the inaugural Institute Leadership Development Program (2011-2012)

## 2012 Publications

### REFEREED JOURNAL ARTICLES

1. B.J. Hales, C.E. Elliot, L.Y. Chai, L.J. Pearce, T. Tipayanon, L. Hazell, S. Stone, S. Piboonpocanun, W.R. Thomas W-A Smith. Quantitation of IgE binding to the chitinase and chitinase-like house dust mite allergens Der p 15 and Der p 18 compared to the major and midrange allergens. *Int Arch Allergy Immunol.* 2012 Oct 16;160(3):233-240. Impact Factor (IF): 2.54
2. S.T. Yerkovich, B.J. Hales, M.L. Carroll, J.G. Burel, M.A. Towers, D.J. Smith, W.R. Thomas, J.W. Upham. Reduced rhinovirus-specific antibodies are associated with acute COPD exacerbations. *BMC Pulm Med.* 31;12(1):37. [Epub ahead of print], 2012. IF: 2.42
3. B.J. Hales, L.Y. Chai, C.E. Elliot, L.J. Pearce, G. Zhang, T.K. Heinrich, W-A Smith, M.H. Kusel, P.G. Holt, P.D. Sly and W.R. Thomas. Anti-bacterial antibody responses associated with the development of asthma in house dust mite-sensitised and non-sensitised children. *Thorax.* 67:321-7, 2012 IF: 6.84
4. A.H.J. van den Biggelaar, W.S. Pomat, S. Phuanukoonon, A. Michael, C. Aho, M.A. Nadal-Sims, C.J. Devitt, B.J. Hales, W-A Smith, T. Mitchell, S. Wiertsema, P. Richmond, P. Siba, P.G. Holt, D. Lehmann. Effect of early carriage of *Streptococcus pneumoniae* on the development of pneumococcal protein-specific cellular immune responses in infancy. *Pediatr Infect Dis J.* 31:243-8, 2012. IF: 3.58

### CONFERENCE ABSTRACTS

1. J. Iwasaki, W-A Smith, W.R. Thomas, B.J. Hales. Sero-epidemiology of Human Rhinovirus C. American Thoracic Society International Meeting, *Am J Respir Crit Care Med* 185: A3293, 2012.
2. W. R. Thomas, W-A Smith, B.J. Hales. The IgE and IgG antibody profile of the known spectrum of protein cat allergens. 29th Symposium of the Collegium Internationale Allergologicum; A133, 2012
3. F. L Jahnsen, E. Danilova, F-E. Johansen, C. Hoffmann, I. Skrindo, E. Gran, J. Jahnsen, B.J. Hales, W-A. Smith. A role for CCL28-CCR3 in T cell homing to the upper airway mucosa. 29th Symposium of the Collegium Internationale Allergologicum; A56, 2012
4. M. Larché, J.Y. Mu, L. Wiltshire, C. Kipling, W-A Smith, B. J. Hales, W.R. Thomas, R. P. Hafner. Fel d 1 peptide immunotherapy for cat allergy is associated with IL-10 production to multiple cat allergens. 29th Symposium of the Collegium Internationale Allergologicum; A163, 2012

# PAEDIATRIC RESPIRATORY PHYSIOLOGY

## Overview

The Paediatric Respiratory Physiology research group was established in mid 2010 with the appointment of A/Prof Graham Hall by the Telethon Institute of Child Health Research. The primary aim of the group is the assessment of lung growth and development in both health and in respiratory disease, including asthma, cystic fibrosis and chronic lung disease of prematurity.

## Cystic Fibrosis

### CYSTIC FIBROSIS OVERVIEW

Imagine a world where you often have to miss school, playing sport and fun times with friends because your lungs don't work properly. You have to spend hours each day having treatments and getting a cold could potentially mean having to be admitted to hospital. This is what life can be like if you are child with cystic fibrosis (CF). CF is the most common chronic, life-shortening genetic condition affecting Australians. Approximately 1 in 25 people carry a CF-causing gene, resulting in around 1 in 2000 babies being born with the disease. CF affects many body systems, but is most devastating in the lungs, reducing a child's quality of life, and eventually leading to premature death.

AREST CF is a collaborative group of over 30 doctors, allied health professionals and researchers dedicated to improving the respiratory health of children with CF by translating scientific research into tangible clinical outcomes. The WA arm of the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) is based at the Telethon

Institute and is led by Professor Stephen Stick.

### CYSTIC FIBROSIS RESEARCH AREAS

Research by our group and others has shown that infants and children with CF exhibit reduced lung function and evidence of inflammation and infection at a very early age. This highlights the need for new treatments that can be given from time of diagnosis to prevent and/or reverse the damage.

### CYSTIC FIBROSIS EARLY SURVEILLANCE PROGRAM (ESP)

The ESP is the platform upon which the AREST CF research program is based. Children attending CF clinics in Perth and Melbourne participate in the ESP from the time of diagnosis onwards. The ESP includes bronchoalveolar lavage (BAL, to assess airway inflammation, infection and other markers of disease), imaging (CT scan, to measure structural lung disease) and lung function measurements. Researchers are able to track the progress of lung disease through a comprehensive longitudinal set of biological samples, images and data archives. The ESP is now embedded in standard clinical practice in both Australian centres, and is in the process of being adopted by centres in the Netherlands and Switzerland. In 2012, Professor Stick and A/Prof Sarath Ranganathan (VIC) were awarded a grant by US Cystic Fibrosis Foundation Therapeutics to maintain and expand this precious resource.

*Funded by: NHMRC, US Cystic Fibrosis Foundation Therapeutics*

### CYSTIC FIBROSIS EARLY DISEASE

### MECHANISMS

A better understanding of the significant contributing factors to the establishment and progression of CF lung disease will enable researchers to identify key targets for new treatments. Our research into early disease mechanisms combines data and samples from the ESP with cutting edge technologies for measuring airway biology and infection. New research projects in 2012 include investigations into mucus, hypoxia and the respiratory microbiome in progressive CF lung disease with the University of North Carolina, USA (NIH grant awarded in 2012) and the role of bioactive lipids in resolution of inflammation and tissue remodeling with Erasmus Medical Centre, Netherlands.

*Funded by: NHMRC, NIH*

### CYSTIC FIBROSIS PREDICTORS AND ENDPOINTS

The premise that underpins this research area is the identification of early predictors of adverse pulmonary outcomes in children with CF. This will allow treatments to be targeted at those who will benefit the most. Development of objective novel, safe and potentially more informative methods will allow clinicians to identify progressive lung disease earlier and prevent or delay the onset of abnormal lung structure and function. These methods can then be incorporated as outcome measures in clinical trials of new therapeutics. Prof Graham Hall's Paediatric Respiratory Physiology team is a key element of this research, and partnering with A/Prof Sarath Ranganathan (Vic) and Professor Harm Tiddens (Erasmus MC, Netherlands) the

team has been successful in obtaining funding from various sources in 2012 to investigate different aspects of lung structure/function and disease progression.

*Funded by: NHMRC, NIH, UWA, Lung Institute of WA*

### CYSTIC FIBROSIS DEVELOPING AND TRIALING NEW TREATMENTS AND INTERVENTIONS

A new research area for the group is the development of a stem cell program aimed at producing respiratory epithelial cells. These cells could be used to test candidate therapeutic compounds as well as a therapy to replace defective epithelial cells in CF patients. This program is being led by Dr Anthony Kicic, in partnership with researchers from UWA, Monash University and WEHI.

In March 2012, Professor Stick led a workshop sponsored by key international stakeholders. The workshop is the first stage of a collaborative process to reach consensus on clinical trial outcomes for young children with CF and to develop a research framework that addresses gaps in knowledge. Professor Stick proposed that COMBAT CF clinical trial, the first interventional trial for prevention of lung disease in infants, be adopted by this group as a template for trials of new therapeutics. Our goal is to eventually ensure that a clinical trial is available to every child born with CF.

*Funded by: NHMRC, US Cystic Fibrosis Therapeutics*

### CYSTIC FIBROSIS PSYCHOSOCIAL EFFECTS OF EARLY INTERVENTIONS

Little is known about the psychological, social and economic effects on families of children undergoing early interventions for CF. Examination of the risks, burdens and benefits for families will inform improved future strategies for appropriate clinical and pastoral care. Translation of this research will also impact on content and delivery of education, nature of support services offered and development of relationships between families and providers, improving service delivery and potentially health outcomes for children with CF. Collection of qualitative and quantitative data from parents and care-givers of children participating in the ESP commenced in 2012 under the leadership of Dr Tonia Douglas, CF Centre Director at Princess Margaret Hospital.

*Funded by: NHMRC, WA Department of Health*

## EVOLUTION OF AIRWAY FUNCTION AND INFLAMMATION IN EARLY CF LUNG DISEASE

GRAHAM HALL, STEPHEN STICK, SARATH RANGANATHAN (VIC), KATHRYN RAMSEY AND TIM ROSENOW AS PART OF THE AREST CF COLLABORATION (WWW.ARESTCF.ORG)

Cystic Fibrosis (CF) is a condition of chronic inflammation and infection resulting in destruction of lung architecture eventually leading to death. We and others have shown that infants and young children with CF show evidence of early inflammation and infection and reduced lung function highlighting this as a crucial period for intensive and new treatments to prevent progression or even reverse lung disease. However, the evolution of peripheral airway pathology in early infancy

is poorly understood and ongoing relationships between peripheral respiratory function and measurements of pulmonary inflammation or infection remain unknown. The goals of this study are to evaluate objective measurements of respiratory function and their combined ability to detect and monitor the presence of lung disease early in the life of infants and young children with cystic fibrosis.

*Funded by NHMRC, USA Cystic Fibrosis Foundation*

## Indoor air pollution and lung health

### IMPACT OF EXPOSURE TO AIR POLLUTANTS DURING THE PRENATAL PERIOD ON LUNG FUNCTION IN INFANCY

GRAHAM HALL, PETER FRANKLIN, ZOLTAN HANTOS AND MARK TAN WITH THE PEEL CHILD HEALTH STUDY (WWW.PEELCHILDHEALTHSTUDY.COM.AU)

This project aims to assess the impact of prenatal environmental exposures on lung function in infancy. In particular we wish to:

- Determine the impact of air pollution, particularly indoor air pollution, during the prenatal period on lung function in infancy.
- Investigate the different measures of infant lung function for detecting early lung changes in response to prenatal environmental exposures.
- Assess the impact of early life exposure to air pollution on respiratory symptoms during infancy

*Funded by NHMRC*

## Long term outcomes following preterm birth

### INVESTIGATION OF THE INFLUENCE PRETERM BIRTH ON LUNG STRUCTURE AND FUNCTION IN SCHOOL AGE CHILDREN

GRAHAM HALL, ANDREW WILSON, JANE PILLOW, ANDREW MAIORANA, SHANNON SIMPSON, KARLA LOGIE, CHRIS O'DEA.

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of premature birth. Contemporary BPD is dominated by peripheral lung abnormalities including failed alveolarisation with a decreased number of large and simplified alveoli and abnormal pulmonary vascular development. The few studies to examine the long term respiratory outcomes in new BPD have demonstrated impaired gas transfer reduced cardiopulmonary exercise capacity, gas trapping and increased respiratory morbidity. None of these studies undertook a comprehensive assessment of lung structure, peripheral lung function and respiratory morbidity and examined the influence of neonatal history on the long term outcomes of new BPD. Studies of this nature are essential and will provide an improved understanding of the pathology of new BPD and its long term outcomes and allow a more targeted approach to the treatment and management of infants with BPD through the neonatal period and into childhood.

Key outcomes include

- All preterm children have abnormal lung structure, irrespective of the presence of BPD.

- Children with a history of BPD are twice as likely to exhibit exercise flow limitation when compared to preterm children without BPD.
- Preterm children (with and without BPD) had reduced lung function. Specifically, significant reductions in spirometry, gas trapping and altered peripheral lung mechanics.
- Respiratory Symptoms are increased in preterm children irrespective of a diagnosis of BPD. Children with respiratory symptoms in the last year had worse lung function outcomes than children without recent symptoms

*Funded by NHMRC, Raine Foundation and Princess Margaret Hospital Foundation*

## Asthma

### RISK FACTORS FOR THE DEVELOPMENT OF LATE ONSET AND PERSISTENT ASTHMA IN YOUNG ADULTS: A LONGITUDINAL BIRTH COHORT STUDY

ELISHA WHITE, NICK DE KLERK, PAT HOLT, ZOLTAN HANTOS, ELYSIA HOLLAMS AND GRAHAM HALL

Australia has one of the highest incidences of asthma in the world, with 14-16% of children and 10-12% of adults diagnosed as asthmatic. Early-life factors involved in the development of childhood asthma have been well explored however it remains largely unknown whether these risk factors, or other yet unidentified factors, are involved in the development of later onset asthma or persistence of



childhood asthma into adulthood. This study is investigating the contributions and interactions between atopic status, immunophenotype, inflammation, respiratory health, pulmonary function and airway hyperresponsiveness in the development of later-onset asthma and persistence of childhood asthma in 23 year old participants of the Western Australian (Raine) cohort group. If risk factors for the development of later-onset asthma and persistent childhood asthma are present during early life, and are able to be identified in this study, this could provide much needed resources in the ongoing effort to effectively treat or even prevent adult asthma, and reduce the significant health and financial burden that asthma places upon individuals and their communities.

*Funded by National Health and Medical Research Council*

## MEASUREMENT OF BRONCHIAL HYPER-RESPONSIVENESS IN YOUNG CHILDREN: MANNITOL AND EXERCISE CHALLENGE TESTING

GRAHAM HALL, SHANNON SIMPSON AND AFAF ALBLOUSHI

Summary: The addition of objective measures of bronchial hyper-responsiveness (BHR) to current clinical practice may result in improved diagnosis and management of young children with exercise related symptoms. This project aims to determine the feasibility of BHR testing using the forced oscillation technique (FOT) as a primary outcome of the mannitol challenge test in pre-school children with exercise induced symptoms. In addition we aim to determine the agreement of the mannitol challenge test and

exercise challenge test in these children.

### Key Outcomes in 2012

We found that 85% of children aged three to seven years and 100% of children aged 4-7 years were able to complete the mannitol challenge using FOT as the outcome measure. The three children that failed to complete the test were three years of age and did not complete due to difficulty sustaining attention.

Further research comparing mannitol and exercise challenge tests and to define appropriate cut off levels to support the diagnosis of exercise induced bronchoconstriction in young children is ongoing

*Funded by: Asthma Foundation of WA and Australian and New Zealand Society of Respiratory Science*

## Staff and Students

### HEAD OF DIVISION

Graham L. Hall; BAppSci, PhD, CRFS, FANZSRS

Professor (Adjunct), Centre for Child Health Research, University of Western Australia

Associate Professor (Adjunct), Faculty of Health Sciences, Curtin University

Senior Respiratory Scientist in Charge, Respiratory Medicine, Princess Margaret Hospital

### RESEARCH STAFF

Ms Georgia L Banton BSc – Research Assistant

Mr Chris O’Dea B. Med Sci (Resp Hsci) Hons –

Senior Respiratory Scientist

Ms Judy Park BSc MBIostat

Ms Kathryn Ramsey BSc (Hons) – Research Officer

Dr Shannon Simpson PhD – Research Officer

Ms Maureen Verheggen M Med Sci – Senior Respiratory Scientist

Dr Andrew Wilson Paediatric Respiratory Physician

### POSTGRADUATE STUDENTS

Ms Afa Al Bloushi BSc - PhD Candidate

Ms Karla M Logie BSc(Hons) - PhD Candidate

Mr Chris O’Dea PhD, B. Med Sci (Resp Sci) Hons - PhD Candidate

Mr Tim Rosenow BSc Grad Cert Paed Resp Sci – PhD Candidate

Mr Mark Tan MSc - PhD Candidate

### Awards

Chris O’Dea  
“Excellence in respiratory measurements” at ANZSRS ASM  
Curtin Award at ASMR WA annual symposium

Kathryn Ramsey  
Lung Institute of WA Glenn Brown Memorial Grant

Shannon Simpson

Thoracic Society of Australia and New Zealand  
Peter Phelan Travel Fellowship

Awarded to attend the American Thoracic Society meeting (San Francisco) and visit the laboratory of Prof Zoltan Hantos, Hungary.

TSANZ Travel Award  
Awarded to attend the annual scientific meeting (Canberra)

University of Western Australia Research Development Award  
“Assessing the Impact of Posture on the Relationship between Ventilation Distribution and Structural Lung Damage in Children with Cystic Fibrosis”

Maureen Verheggen  
WA Respiratory Science Travel Award

## External Committees

### INTERNATIONAL

Graham Hall.  
Joint American Thoracic Society - European Respiratory Society Working Party on Infant Lung Function Testing (2003-Ongoing)

European Respiratory Society Global Lung Initiative Task Force: Co-Chair (2008 - 2012)

Joint American Thoracic Society - European Respiratory Society Task Force for Provocation testing guidelines (2010 -Ongoing)

European Respiratory Society Annual Congress Paediatric Respiratory Physiology Abstract review committee

Associate Editor; Respirology (Oct 2012 –

Ongoing)

Editorial Advisory Panel; Expert Review of Respiratory Medicine (Oct 2006 – Ongoing)

Secretary; Paediatric Respiratory Physiology Group, European Respiratory Society (Sep 2012 – Ongoing)

## NATIONAL

Graham Hall

Thoracic Society of Australia and New Zealand Professional Standards Sub-committee (2008 - )

Andrew Wilson

Member Medical and scientific advisory committee, Asthma Australia (2011 – )  
Board Member, Thoracic Society of Australia and New Zealand (TSANZ). April 2011 – April 2012.  
Chair, Local organising committee TSANZ annual scientific meeting Perth 2011.  
Co-ordinator of Paediatric Training, Specialist Training Committee for Thoracic and Sleep Medicine, Royal Australasian College of Physicians (RACP) (2008 – )

## LOCAL

Graham Hall

Asthma Foundation of Western Australia Board member (2010 – )

Andrew Wilson

Thoracic Society of Australia and New Zealand WA state committee: Branch President 2008 – 2011

## Invited Presentations

Graham Hall

2012

TSANZ: Laboratory Accreditation workshop

2012

ATS Postgraduate Course: Case based: Pulmonary function test interpretation “Interpreting Lung function in Children”

2012

ERS Symposium: “Reference values for paediatric pulmonary function testing: Glee about GLI “

2012

ERS Symposium: What lung function test is best for managing young children with BPD

Shannon Simpson

Thoracic Society of Australia and New Zealand, WA scientific meeting

Rising Stars of Respiratory Science session “Pulmonary infection in infants with cystic fibrosis leads to progressive ventilation inhomogeneity”

## ACTIVE collaborations

Royal Perth Hospital, Respiratory Medicine, Perth

Dr Kevin Gain

King Edward Memorial Hospital, Neonatology, Perth

Prof Jane Pillow

Assoc Prof Noel French and Dr R Hagan

Dr Mary Sharp

University of Western Australia, Perth

A/Prof Dr Peter Franklin

A/Prof Sunalene Devadason

Royal Children’s Hospital, Melbourne

Dr Sarath Ranganathan

University Children Hospital, Zurich Switzerland

Dr Alex Moeller

University Children Hospital, Vienna Austria

Dr Fritz Horak

Institute for Child Health, London UK.

Prof Janet Stocks

University of Szeged, Hungary

Prof Zoltan Hantos

Erasmus University, Rotterdam, The Netherlands

Prof Philip Quanjer

# POPULATION SCIENCES

## Overview

Researchers within the Division of Population Sciences undertake multidisciplinary research projects with a focus on developmental health, mental health, nutrition, indigenous health, developmental disorders, childhood cancer and improving services for children and families. Almost 200 staff and students make up the Division with expertise in a number of fields including epidemiology, developmental psychology, biostatistics, medicine, sociology and other social sciences. Research is conducted collaboratively with partners in government as well as non-government organisations and community groups. Our overall aim is to promote and maintain the health and development of children, as well as supporting and enhancing their social, emotional, academic, and vocational wellbeing.

Researchers within the Division apply a range of research methods to answer research questions. These methods can be quantitative such as analysis of complex linked databases with the view of identifying patterns and trends in child health or they can be qualitative methods such as involving participatory action research, focus groups and the exploration of the views and perceptions of community members.

The Division is committed to making a difference to the lives of children and families in Western Australia, nationally and internationally. This commitment is seen by our working relationships and collaborations with government (for example: Health, education, child protection, disability) and our community partnerships. These collaborations aim to ensure

that we are addressing relevant and translatable research questions as well as addressing issues that are relevant to the Western Australian community. This means we have a greater chance of improving the lives of Western Australia children and families.

## Highlights for 2012

In January, researchers from the Division found that the consumption of sugary drinks is high amongst Australian children and adolescents with the majority of these drinks consumed in the home. The study involving a representative random sample of 4,834 Australian children aged 2 to 16 years as part of the 2007 Australian National Children's Nutrition and Physical Activity Survey found that less than 20% of sugary drinks consumed by children and adolescents were sourced from school canteens or fast food outlets.

The study team said parents and children need to be educated about the consequences of high consumption of both carbonated and non-carbonated sugary drinks as they contribute to obesity as well as nutrition-related chronic disease. The study team also found that older children tended to drink more carbonated and sports drinks, while younger children drank more juice with added sugar and cordial. While children whose parents had higher levels of education consumed less carbonated drinks, these children still consumed high quantities of sweetened juice and flavoured milk which are still high in sugar.

Also in January, a researcher from the Division found that boys who are exposed to high levels

of testosterone before birth are twice as likely to experience delays in language development. The study used umbilical cord blood to explore the presence of testosterone when the language-related regions of a fetus' brain are undergoing a critical period of growth. The finding is significant in that it gives a biological explanation for why boys language development differs to that in girls. While language development varies between individuals, boys tend to develop later and at a slower rate than girls. The purpose of the research was to test whether this could be due to prenatal exposure to sex-steroids such as testosterone. Male fetuses are known to have 10 times the circulating levels of testosterone compared to females. The team proposed that higher levels of exposure to prenatal testosterone may increase the likelihood of language development delays. The results of this study showed boys with high levels of testosterone in cord blood were between two-and-three times more likely to experience language delay than boys with normal levels of testosterone. However, the opposite effect was found in girls, where high-levels of testosterone in cord blood were associated with a decreased risk of language delay.

In February, researchers within the Division were recognised as one of the Ten of the Best Research Projects of 2011 by the National Health and Medical Research Council (NHMRC). The \$8 million grant over five years funded research teams led by the Division's most experienced and respected health researchers including Professors Fiona Stanley, Steve Zubrick, Carol Bower, Nick De Klerk, Sven Silburn, Associate Professor Deborah Lehmann and Dr Helen Leonard.

Some of the group's achievements include:

- evidence to support the fortification of bread with folate to reduce serious birth defects like spina bifida
- evidence to underpin the new national guidelines for consuming alcohol in pregnancy
- initiatives to reduce serious infections like pneumonia and gastroenteritis in Aboriginal children
- research to support the introduction of a vaccine to cut the incidence of Hib meningitis
- establishing a cerebral palsy register that has now been adopted nationally to better understand the causes, most effective treatments and services
- better understanding trends and causes of autism spectrum disorders
- documenting a rise in common form of birth defect - hypospadias
- development of an index of early child development for Australia that has now been rolled out nationally.

This program of research has generated more than 360 journal articles, nine books and 30 book chapters. The program grant team has also made significant contributions to the understanding and diagnosis of fetal alcohol syndrome, otitis media and other ear diseases in Aboriginal children, metabolic syndrome, adolescent fatty liver disease and psychological problems. It has established the value of first trimester screening for chromosomal disorders in WA and the risk of birth defects in children

born following assisted conception.

Also in February, a research study found that children of mums who had low levels of Vitamin D during pregnancy are twice as likely to have language difficulties. The research is the largest study of its kind into the link between a mother's vitamin D levels and the effect on her child's speech and behavioural development. The study looked at Vitamin D concentrations during the pregnancies of more than 740 women, with follow up investigations of their child's development and behaviour at regular periods up to 17 years of age. The findings of this study are significant, given that Vitamin D levels among women are known to have decreased steadily over the past 20 years. This study has significant implications in that it could provide an early intervention to prevent some language difficulties.

In March, a researcher in the area of Down Syndrome within the Division was recognized as the recipient of a prestigious West Australian research scholarship. 25 year old Kitty Foley has been awarded the 'Stan Perron Award for Excellence' for her work over the past year investigating the transition from high school to adulthood for young people with Down syndrome. The award is one of a number of scholarships supported by the 'Stan Perron Charitable Foundation' recognizing the work of exceptional postgraduate students who are undertaking their research at the Telethon Institute for Child Health Research. Kitty's interest in Down syndrome began through her work as an Occupational Therapist focusing on children with intellectual and developmental disabilities.

In April, researchers from the Division joined more than 50 scientists from 36 research institutions around the world to improve early nutrition to boost long-term health. Coordinated by the Hauner Children's Hospital, University of Munich, EarlyNutrition, brings together a multidisciplinary team of internationally acknowledged scientists, with significant experience in complementary areas of nutrition, child and maternal health. Researchers within the Division are confident that this project will have a significant impact on how obesity and related health conditions are treated. The research will help develop an international set of recommendations about the key components of nutrition in babies and children that give them the best basis for adult health. Western Australia's Raine Study, which is based at the Telethon Institute, is one of the largest and most successful studies of pregnancy, childhood, adolescence and young adulthood anywhere in the world and, will be a uniquely valuable resource over the course of this investigation.

In June, a Divisional researcher, Associate Professor Deborah Lehmann dedicated to reducing serious chest and ear infections in children was recognized with the award of Officer in the Order of Australia (AO). Associate Professor Deborah Lehmann heads infectious diseases research within the Division. Dr Lehmann prior to joining the Division, spent a number of years in PNG where she headed the Pneumonia Research Program of the PNG Institute of Medical Research, undertaking studies of the epidemiology of respiratory infections and trials of pneumococcal and Hib vaccines. In 1998 Deborah moved to the Telethon Institute for Child Health Research

and has been working in the Division on otitis media, pneumococcal infections, the evaluation of swimming pools in remote Aboriginal communities and factors that contribute to lower respiratory tract infections.

In September, a new study by Divisional researchers found that young children with severe or persistent asthma are at higher risk of developing many common mental health problems. The research, a collaboration between researchers at Perth's Telethon Institute for Child Health Research and Columbia University in New York found that as the severity of asthma increases, so do problems such as anxiety and depression. The study used Western Australian data from the Raine Study to determine whether children who had asthma at age 5 were vulnerable for later mental health problems through to the age of 17 years. The research team found that having asthma at age 5 was associated with a higher vulnerability for the later development of problems such as anxiety, conduct problems and affective problems. The findings of this study support the need to assess psychological functioning as part of routine care for children with a chronic or severe disease, including for those with severe and persistent asthma throughout childhood.

Also in September, a research team within the Division announced that they had been awarded a contract to lead and undertake a comprehensive national survey of the mental health of Australia's children. This 2nd Child and Adolescent Component of the National Survey of Mental Health and Well-being will take place between May and September 2013, gathering information about the mental health status of approximately 5000 children aged between 4-17

years from across Australia. The survey is funded by the Australian Government Department of Health and Ageing, and is the first national survey of its type in 15 years. The survey will be headed by University of Western Australia Professors Stephen Zubrick and David Lawrence who are both part of the Division. This study will provide valuable new information on emotional and behavioural problems in children in a new millennium and will provide new information to allow appropriate policies and planning and to enable families and communities to better respond to need and to better implement promotion and prevention strategies.

Also in September, a study by Divisional researchers has uncovered a significant decline in the risk of birth defects amongst WA children born using Assisted Reproductive Technology (ART). The study, using data up to 2002 showed a large decrease in the rate of birth defects compared to an earlier study carried out by the same researchers using data from the mid-1990's. The more recent study, which included data up until 2002, showed the risk of birth defects amongst single babies born using Assisted Reproductive Technology in WA dropped from 10.9% between 1994 and 1998 to 7.5% in the four years following (1998-2002), compared with a rate of 5.2% in the naturally conceived group. Twins born via assisted pregnancies also showed a similar pattern of decreasing risk from the first time period to the second. This study suggests an encouraging decline in major birth defect prevalence in children born as a result of assisted pregnancies in Western Australia. Changes to clinical practice may be largely responsible with improved culture media and better culture and storage

conditions leading to the transfer of 'healthier' embryos.

The final achievement of September for the Division was the release of the results of a study by Divisional researchers that found folic acid supplements before and during pregnancy reduces the risk of childhood brain tumours. The national case-control study collected data between 2005 and 2010 to investigate nutritional, environmental and genetic risk factors for childhood brain tumours. 335 mothers of children with brain tumours participated in the study along with 1363 mothers of healthy control children, randomly recruited from around Australia. While other studies had investigated the impact of multivitamin supplements, this research project was the first to separate out different types of supplements, including folic acid and other B group vitamins. This study found that folic acid use before pregnancy reduced the risk of childhood brain tumours by around 30%. The results also suggest some effect of folate taken after conception, but it was not as strong as when taken before pregnancy.

In October 2012, Divisional researchers uncovered a significant link between vitamin B levels and the mental health and wellbeing of children and adolescents. The research indicated that children with a diet low in B-vitamins were more likely to experience mental health and behavioural problems than those with a healthier diet rich in B-vitamins. The study is the first to report on a direct link between the prevalence of externalising behaviour problems in adolescents at 17 years and a reduced intake of B1, B2, B5, B6 and folate. B-vitamins are essential for the

production of neurotransmitters, like serotonin, which modulates behaviour in humans and can contribute to feelings of well-being and happiness. Previous studies have shown that externalising mental health and behaviour problems developed during adolescence are related to a higher risk of offending and substance abuse later in life. This study looked at the relationship between diet, specifically B-vitamin intake and the presence of these externalising behaviours. The findings of this study reinforce how a healthy diet can play a key role in improving mental health outcomes for young people.

## Birth Defects and Developmental Disorders

### ALCOHOL AND PREGNANCY

In 2012, the Alcohol and Pregnancy team developed a strategic plan for the Alcohol and Pregnancy and FASD Research Group, establishing priorities for our research for the next 3 years that are based on diagnosis and management of FASD, workforce development and community engagement and are focused on translation of research into practice and policy that will make a positive difference to children and families.

Driving the agenda for FASD in Australia over the next five years will be the reports of the House of Representatives Standing Committee on Social Policy and Legal Affairs Inquiry into Foetal Alcohol Spectrum Disorder; the Western Australian Government Health Standing Committee Inquiry into improving educational outcomes for Western Australians of all ages

(specifically item 5 *Fetal Alcohol Syndrome*), and the Australian Fetal Alcohol Spectrum Disorders Action Plan 2013-2016 from the Foundation for Alcohol Research and Education (FARE), all published in 2012. Members of the Alcohol and Pregnancy and FASD Research Group made written submissions and appeared before the Government Committees at public hearings and are committed to seeing that the recommendations are implemented and that there are benefits to people living with FASD, their families and the community.

In February 2012 the Telethon Institute and Drug and Alcohol Office (DAO) held a Focus on Fetal Alcohol Spectrum Disorder (FASD) in WA Forum. With 155 people registered to attend we were overwhelmed by the interest in the forum and the positive feedback we received. Participants were from government departments - corrective services, child protection, education and health; maternity groups and support services; universities; research institutes; Aboriginal health organisations; foster carers and support organisations; community groups; private practitioners; and consumers and community members. Presentations included information on initiatives and programs from Kununurra, Fitzroy Valley, Perth, Bunbury and Esperance.

FARE and Public Health Association of Australia in association with the Telethon Institute, University of Sydney, University of Queensland, Alcohol HealthWatch New Zealand, NOFASARD and the Russell Family Fetal Alcohol Disorders Association commenced work on the Australasian FASD Conference 'Time to learn, time to act' to be held in November 2013. This conference aims to share knowledge about FASD and bring people together to exchange ideas,

practice, research and policy discourse. The Telethon Institute has one representative on the Conference Organising Committee and two representatives on the Stakeholder Advisory Group.

## Alcohol and Pregnancy: Educational Resources for Health Professionals

### FOLATE AND PREVENTION AND NEURAL TUBE DEFECTS

CAROL BOWER, HEATHER D'ANTOINE, SUSANNAH MAXWELL, KATE BRAMELD, SIOBHAN HICKLING, JULIA MARLEY, PETER O'LEARY.

In September 2009, Australia implemented mandatory folic acid fortification of wheat flour for bread-making to reduce the incidence of neural tube defects. Aboriginal infants have a higher risk of neural tube defects than non-Aboriginal infants in Australia. We undertook a study to estimate baseline folate status (prior to fortification). We recruited participants from people presenting to health services in the metropolitan area and two regional areas (159 non-Aboriginal and 191 Aboriginal participants). Participants completed a short questionnaire and had blood taken to measure red blood cell (RBC) folate and serum vitamin B12.

One in ten Aboriginal women participants and a quarter of the Aboriginal male participants had low RBC folate (below 250 ng/mL). None of the non-Aboriginal women and 4% of the non-Aboriginal men had low RBC folate concentrations. All participants were vitamin B12 replete. Although few Aboriginal and

non-Aboriginal women aged 16–44 reported consumption of folic acid supplements, shop-bought bread consumption was high. The higher prevalence of folate deficiency in Aboriginal participants and their frequent consumption of shop-bought bread suggest that they are likely to benefit from a universal program of folate fortification. Trends in neural tube defects are being monitored, but because of the small number of Aboriginal births, the findings from this baseline study, compared with data from a repeat study to be conducted in 2013, will provide earlier evidence of the effect of mandatory fortification on folate status.

### DEVELOPMENT OF A DIAGNOSTIC INSTRUMENT FOR FETAL ALCOHOL SPECTRUM DISORDERS IN AUSTRALIA (FASD PROJECT)

WINTHROP RESEARCH PROFESSOR CAROL BOWER & PROFESSOR ELIZABETH ELLIOTT AM (LEAD INVESTIGATORS), DR ROCHELLE WATKINS & HEATHER JONES (PROJECT STAFF) AND THE STEERING GROUP: DR LUCINDA BURNS, MAUREEN CARTER, HEATHER D'ANTOINE, DR JAMES FITZPATRICK, ASSOC. PROF JANE HALLIDAY, LORIAN HAYES, ASSOC. PROF JANE LATIMER, ANNE MCKENZIE, SUE MIERS AM, DR RAEWYN MUTCH, DR COLLEEN O'LEARY, JAN PAYNE, DR ELIZABETH PEADON, ELIZABETH RUSSELL, DR AMANDA WILKINS.

An updated final report was submitted to the Department of Health and Ageing in May 2012. Three papers based on the research have been published, one is awaiting publication and a further two papers are being finalised for submission to relevant journals.

*Funders of the project: Department of Health*

*and Ageing; NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).*

### EVALUATION OF INFORMATION AND SERVICES FOR PARENTS/CARERS OF CHILDREN WITH A FETAL ALCOHOL SPECTRUM DISORDER

DR AMANDA WILKINS (LEAD INVESTIGATOR), HEATHER JONES, DR ROCHELLE WATKINS AND WINTHROP RESEARCH PROFESSOR CAROL BOWER

Research funded by the Foundation for Alcohol Research and Education (FARE) and conducted by the Telethon Institute for Child Health Research evaluated a wide range of resources that aim to help parents and carers of people with Fetal Alcohol Spectrum Disorders (FASD) in Australia.

The study showed that while foster carers are highly committed to the children in their care, they often felt that the complex needs of their children were not adequately supported, which was a significant contributing factor to their stress and fatigue.

A final report was submitted to FARE in August 2012. The full report and a summary report can be viewed at <http://alcoholpregnancy.childhealthresearch.org.au/>

*Funder of the project: Foundation for Alcohol Research and Education (FARE)*

### KNOWLEDGE, ATTITUDES AND PRACTICE OF FASD WITHIN THE WESTERN AUSTRALIAN CRIMINAL JUSTICE SYSTEM

DR RAEWYN MUTCH (LEAD INVESTIGATOR), DR ROCHELLE WATKINS, HEATHER JONES AND WINTHROP RESEARCH PROFESSOR CAROL BOWER

A study of the Western Australian justice system identified that up to 85% of staff say responding to the needs of people with Fetal Alcohol Spectrum Disorders (FASD) is an issue in their work.

The report by the Telethon Institute and funded by the Foundation for Alcohol Research and Education (FARE) recommends greater awareness, better training and education and alternate sentencing options that consider the neurocognitive impairments associated with FASD.

A final report was submitted to FARE in November 2012. The full report and a summary report can be viewed at <http://alcoholpregnancy.childhealthresearch.org.au/>

*Funder of the project: Foundation for Alcohol Research and Education (FARE)*

### PHARMACOVIGILANCE IN PREGNANCY USING POPULATION-BASED LINKED DATASETS

LYN COLVIN, LINDA SLACK-SMITH, FIONA STANLEY, CAROL BOWER

New medicines are not usually trialled on pregnant women before release so it is important to have ways to monitor their safety. This project uses data linkage of population-based health datasets from Western Australia and the national pharmaceutical claims dataset, the Pharmaceutical Benefits Scheme, to investigate pregnancy outcomes for women

and their children (N=96,698 pregnancies). Medicines are analysed by drug category and at the individual medicine level.

The prescribing of proton pump inhibitors in pregnancy is increasing. We found that the women dispensed a proton pump inhibitor were more likely to be aged 35 to 45 years, have smoked during their pregnancy, to have a multiple birth, reside in a lower socio-economic area, and to have chronic hypertension or asthma. These women were at a higher risk of a postpartum haemorrhage, and were more likely to have a Caesarean delivery. Their children were more likely to weigh < 2500 g, and to be born preterm. There was no significantly increased risk found for any category of birth defect.

Linked administrative data is an important means of pharmacovigilance in pregnancy in Australia. Data linkage provides a rich resource at a relatively low cost and in a more timely manner, than other pregnancy studies in pharmacovigilance whilst maintaining confidentiality.

*Funders of the project: Australian Postgraduate Award (LC).*

*NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).*

### ASSISTED REPRODUCTIVE TECHNOLOGY AND BIRTH DEFECTS

MICHELE HANSEN, JENNIFER KURINCZUK, NICHOLAS DE KLERK, PETER BURTON, ELIZABETH MILNE AND CAROL BOWER

Children born following Assisted Reproductive Technology (ART) treatment currently represent

3.6% of Australian births and there has been an important shift in this country towards the transfer of a single embryo per treatment cycle resulting in fewer multiple pregnancies and leading to major improvements in perinatal outcomes after ART. Using data linkage of the statutory Reproductive Technology Register and other population-based health datasets from Western Australia, we investigated the prevalence of birth defects in children born following ART treatment from 1994 to 2002. This extended our previous study on birth defects in ART infants which had shown a two-fold increased risk of a major birth defect being diagnosed by one year of age. For our more recent study we had information on the total population of ART and non-ART births and any birth defects diagnosed to six years of age, as well as information on all terminations of pregnancy for fetal anomaly during the study period.

There were 2,911 ART and 210,997 non-ART births and terminations of pregnancy for fetal anomaly over the study period. A major birth defect was diagnosed in 8.7% of ART and 5.4% of non-ART singletons (OR 1.5; 95% CI 1.3-1.8), as well as 7.1% of ART twins and 5.9% of non-ART twins of unlike sex (OR 1.1; 95% CI 0.8-1.5). The study confirmed earlier reports of increased cardiovascular, musculoskeletal, genital and gastrointestinal defects in ART infants as well as more recent reports of an increased risk of conditions such as Beckwith Weideman Syndrome and Angelman Syndrome that may be caused by imprinting defects.

Few studies have examined changes in birth defect prevalence over time in ART infants despite the many changes that have occurred

in ART laboratory techniques and patient case-mix. The prevalence of birth defects in ART singletons and twins decreased markedly over the study period. This change was evident across all three clinics contributing data over the whole study and was particularly marked for children conceived as a result of IVF. Changes to clinical practice may be largely responsible with improved culture media and more optimal culture conditions leading to the transfer of "healthier" embryos. Analysis of more recent data is required to examine the health of children born following extended embryo culture and the increased use of embryo cryopreservation.

We have also updated our previous systematic review and meta-analysis of the ART and birth defects literature, published in 2005. Our earlier review found a 30-40% increased risk of birth defects in ART infants. In updating these data we were interested to see whether more recent publications also support an increased birth defect risk, whether the pooled estimate may have changed, and whether there were sufficient papers to estimate birth defect risk in ART singletons and multiples separately. We searched Medline, Embase and Current Contents databases (1978-2012). There were 45 cohort studies included in the review. ART infants (n=92 671) had a higher risk of birth defects (RR 1.3; 95% CI 1.2-1.4) compared with naturally conceived infants (n= 3 870 760). The risk further increased when data were restricted to major birth defects (RR 1.4, 95% CI 1.3-1.6) or singletons only (RR 1.4, 95% CI 1.3-1.4). The results for ART multiples were less clear. When all data for multiples were pooled the RR estimate was 1.1 (95% CI 1.0-1.1)

but this increased to 1.3 (95% CI 1.0-1.6) when the analysis was restricted to studies of ART twins where some adjustment was made for differences in zygosity distribution between ART and non-ART multiples. These data are important for the counselling of prospective ART patients.

*Funders of the project: NHMRC Project Grant #211930; NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).*

## THE INFLUENCE OF AMBIENT AIR POLLUTION FROM TRAFFIC EMISSIONS AND PREGNANCY OUTCOMES

GAVIN PEREIRA (ICHR), ANGUS COOK (UWA), NATASHA NASSAR (USYD), CAROL BOWER (ICHR), NICK DE KLERK (ICHR), EVE BLAIR (ICHR), FATIMA HAGGAR (OTTAWA HOSPITAL, CANADA), ANTONIA SHAND (USYD).

The background of our air pollution and pregnancy outcomes research was described in our previous annual report. We published three studies in 2012.

### Study 1: *BMC Pediatrics* 2012, 12:73

The aim of this study was to validate a model for optimal birth weight derived from neonatal records, and to test the assumption that preterm births may be considered optimally grown if they are not exposed to common factors that perturb fetal growth. Weights of fetuses were estimated from serial biometric ultrasound scans (N = 2,848) and combined with neonatal weights for a prospective pregnancy cohort (N = 691). Non-Caucasians, fetuses subsequently born preterm and those with diagnosed or suspected

determinants of aberrant growth were excluded leaving fetuses assumed to have experienced normal growth. A generalised linear longitudinal growth model for optimal weight was

derived, including terms for gestational duration, infant sex, maternal height and birth order. This model was compared to a published model derived solely from birth weights. We found that prior to 30 weeks gestation, the published model yielded systematically lower weights than the model derived from both fetal weight and neonatal weight. From 30 weeks gestation the two models were indistinguishable.

### Study 2: *Occup Environ Med* 2012;0:1-8. doi:10.1136/oemed-2011-100509

Fetal growth restriction has been inconsistently associated with maternal exposure to elevated levels of traffic-related air pollution. We investigated the relationship between an individualised measure of fetal growth and maternal

exposure to a specific marker for traffic-related air pollution. We estimated maternal residential exposure to a marker for traffic-related air pollution (nitrogen dioxide, NO<sub>2</sub>) during pregnancy for 23 452 births using temporally adjusted land-use regression. Logistic regression was used to investigate associations with small for gestational age and sex (SGA) and fetal growth restriction, defined as proportion of optimal birth weight (POBW) below the 10th percentile. Note, the POBW outcome was validated in Study 1 listed above. Sub-populations investigated were: women who spent most time at home, women who did not move house, women with respiratory or circulatory morbidity, women living in low/

middle/high socio-economic areas, women who delivered before 37 weeks gestation, and women who delivered from 37 weeks gestation. We found that an interquartile range (IQR) increase in traffic-related air pollution in the second trimester across all women was associated with an OR of 1.31 (95% CI 1.07 to 1.60) for fetal growth restriction. Effects on fetal growth restriction (low POBW) were highest among women who subsequently delivered before 37 weeks of gestation. Effects on SGA were highest among women who did not move house: OR 1.35 (95% CI 1.08 to 1.69). Larger effect sizes were observed for low POBW than for SGA. Exposure to traffic-related air pollution in mid to late pregnancy was associated with risk of SGA and low POBW in this study.

**Study 3: J Epidemiol Community Health 2012. doi:10.1136/jech-2011-200805**

Pre-eclampsia is a common complication of pregnancy and is a major cause of fetal and maternal mortality and morbidity. Despite a number of plausible mechanisms by which air pollutants might contribute to this process, few studies have investigated the association between pre-eclampsia and traffic emissions, a major contributor to air pollution in urban areas. We investigated the association between traffic-related air pollution and risk of preeclampsia in a maternal population in the urban centre of Perth, Western Australia. The authors estimated maternal residential exposure to a marker for traffic-related air pollution (nitrogen dioxide, NO<sub>2</sub>) during pregnancy for 23 452 births using temporally adjusted land-use regression. This was the same study population as in Study 1 and exposure was assessed by the same methods

as Study 1. Logistic regression was used to investigate associations with pre-eclampsia. We found that each IQR increase in levels of traffic-related air pollution in whole pregnancy and third trimester was associated with a 12% (95% CI 1% to 25%) and 30% (95% CI 7% to 58%) increased risk of pre-eclampsia, respectively. The largest effect sizes were observed for women aged younger than 20 years or 40 years or older, aboriginal women and women with pre-existing and gestational diabetes, for whom an IQR increase in traffic-related air pollution in whole pregnancy was associated with a 34% (95% CI 5% to 72%), 35% (95% CI 0% to 82%) and 53% (95% CI 7% to 219%) increase in risk of pre-eclampsia, respectively. We concluded that elevated exposure to traffic-related air pollution in pregnancy was associated with increased risk of pre-eclampsia. Effect sizes were highest for elevated exposures in third trimester and among younger and older women, aboriginal women and women with diabetes.

**Study 4: Am J Obstet Gynecol 2012;206:74**

For this study, we sought to investigate seasonal variation in fetal growth, accounting for important sociodemographic, biological, and environmental exposures among a much larger population than the previous studies. Records of births 1998 through 2006 in Perth, Western Australia were obtained (N = 147,357). We investigated small for gestational age and sex and the proportion of optimal birth weight (POBW) in relation to seasonal exposures (season, temperature, sunlight) by trimester of pregnancy. Adjustment was made for a wide range of risk factors. The POBW for neonates with third trimesters predominantly in summer was 0.18% (95% CI 0.00 to 0.36%) lower than

for those in winter. POBW decreased by 0.14% (95% CI 0.01 to 0.27%) per interquartile range increase in third-trimester temperature (9.15°C). An interquartile range increase in temperature over pregnancy (0.73°C) was associated with an odds ratio of 1.02 (95% CI 1.00 to 1.05) for small for gestational age and sex. We found that reduced fetal growth was associated with elevated ambient temperatures throughout and late in pregnancy, independently of air pollution and other risk factors.

**Current research**

Through the above research we identified the following gaps in knowledge:

1. That few studies have assessed the influence of traffic-related air pollution on risk of preterm birth that adequately account for underlying individual risk (biological or behavioural).
2. That markers for traffic-related air pollution do not provide information on the specific chemical constituents that biologically contribute to increased risk
3. That adequate exposure assessment is currently limited to developed countries with statutory government monitoring of criteria air pollutants and air toxics.

We are currently undergoing studies to address the above by undertaking a longitudinal study on the risk of air pollution on risk of preterm birth, by assessing the chemical composition of fine particulate matter air pollution (identifying sources), and by investigating the possibility of satellite remote-sensed measures of fine particulate matter derived from modelling the aerial optical depth of the atmosphere.

*Funders of the project: Australian Postgraduate Award, University Postgraduate Award, Perron award, CRC for Asthma and Airways award, Australia China Society for Biomedical Research award, Commercialisation Training Scheme award, UWA GRST grant. <Insert Theme 1 program grant>*

## Intellectual Disability

### INTERNATIONAL RETT SYNDROME STUDY: INTERRETT

HELEN LEONARD, ALISON ANDERSON, AMI BEBBINGTON, NADA MURPHY, STEPHANIE FEHR, JENNY DOWNS, HEIDI MEYER, NAN HU.

The InterRett project is now in its 10th year and continues to be an exemplary model for rare disease research. This project allows clinicians and families caring for an individual with Rett syndrome to directly contribute to the global research effort by completing web or paper-based questionnaires. The resulting data repository, which now contains 2,594 cases, affords investigation of a wide variety of issues and Rett syndrome specific characteristics. Over 20 peer-reviewed papers have been published to date that, for instance, describe: the characteristics that influence diagnosis; pain sensitivity; the influence of DNA variations in the *BDNF* gene on severity; and comparisons of clinical outcomes between those with different types of mutations in the Rett syndrome gene *MECP2*. InterRett currently also includes cases with *MECP2* duplication syndrome who have over expression of the MECP2 protein. Plans are in process to build a separate database which will help generate valuable data for the research community about this newly



described syndrome. International support for the InterRett project continues to strengthen, particularly in China and we have a Chinese national, Nan Hu who is providing translational expertise and assisting families in submitting their information. The InterRett project website was recently updated and includes lay snapshots of our research outcomes and publications. The project website continues to be a valuable tool for case recruitment and dissemination of research output that will be expanded in the year ahead to serve the new MECP2 duplication database project.

*Funders of the project: International Rett Syndrome Foundation*

## TOWARDS EVIDENCE BASED CARE FOR RETT SYNDROME: A RESEARCH MODEL TO INFORM MANAGEMENT OF RARE DISORDERS

HELEN LEONARD, JOHN CHRISTODOULOU, CAROLYN ELLAWAY, LAKSHMI NAGARAJAN, HELEN WOODHEAD, JENNY DOWNS, ELIZABETH GEELHOED, ELIZABETH ELLIOTT, PETER JACOBY, IAN TORODE, GORDON BAIKIE, MARK DAVIS, IAN MCPHEE, MADHUR RAVIKUMARA, SUE THOMPSON, MARGARET THOMSON, AMI BEBBINGTON, AMANDA JEFFERSON, OLIVIA KNIGHT, SONYA GIRDLER, ANNA URBANOWICZ, KINGSLEY WONG, KATHERINE BATHGATE, MEIR LOTAN

Rett syndrome is a rare neurological disorder usually affecting females and caused by a mutation in the *MECP2* gene. AussieRett, as the Australian Rett Syndrome Study is known, is a population-based study which, since 1992, has followed a cohort of Australian Rett syndrome cases born since 1976. The study aims to

describe the natural history of Rett syndrome and assess the impact of the condition on resource utilisation as well as to examine the economic and social burden for families and the community.

In 2011, a three year NHMRC funded study commenced to facilitate best practice in clinical decision making, laboratory procedures and counseling in relation to the diagnosis and management of Rett syndrome. This study aims to:

- develop recommendations for the diagnosis process for Rett syndrome;
- identify longitudinal changes in gross motor abilities, hand function and development of scoliosis and;
- evaluate the clinical effectiveness of scoliosis and gastrostomy surgery in children and adults with Rett syndrome.

For the diagnostic study questionnaires relating to the characteristics of their patients are currently being completed by clinicians who request MECP2 testing from one of the three Australian accredited laboratories. These are completed prior to the result of genetic testing being known. The goal is to develop tools to support clinical decision making to facilitate timely diagnostic testing for girls with Rett syndrome, thereby assisting families in the often stressful early stage when seeking a diagnosis. Data collection has been continuing since July 2011 and will continue through 2013, contact having been made with 125 clinicians throughout Australia thus far.

As part of the longitudinal study follow-up questionnaires were administered in September

2011 to 269 families enrolled in the study and families could return data online, on paper or during a telephone interview. The response fraction from parents and care-workers has been excellent at over 86%. Information has been collected on the affected individual's functional ability in daily living, behaviour, hand function, medical conditions, use of health and education services, and family health and functioning. Questions have also been included to assess parental satisfaction with spinal fusion and gastrostomy procedures for those children and adults who have undergone these procedures.

Scoliosis is a common complication of Rett syndrome, however little is known about the natural history of curve progression and the relationship with the type of genetic mutation, age and mobility level. X-ray data on the progression of the spinal curve of children and adults with scoliosis has started to be collected and will continue throughout 2012.

Spinal fusion (for scoliosis) and gastrostomy insertion (feeding tube into the stomach due to problems with swallowing or poor growth) are surgeries faced by many children and adults with Rett syndrome. The decision to proceed with these surgeries is often difficult for families, and both clinicians and families need accurate information about the short and long term risks and benefits of these procedures. Currently, there are gaps in our knowledge of outcomes. Collection of data from the hospital records has commenced to supplement the questionnaire data and to address these gaps in knowledge and will continue throughout 2013. We are also collecting video data and, during the first five months of data collection, 72 families had already provided video footage of their

daughter's functional abilities. Data collection will continue through 2013.

The AussieRett study has continued to involve consumers through the Consumer Reference Group, biannual newsletters and online via the new website and Facebook page. The Consumer Reference Group, involving family members from across Australia via regular teleconferences, is an opportunity to discuss and give valued feedback on all facets of the study. This year we planned and conducted a national family conference in Brisbane in May 2012, to coincide with the International Child Neurology Conference. The content and running of the conference was guided by family consultation. The conference was attended by 170 family members, carers and therapists, and the many topics were presented by members of the Australian Rett Syndrome Study, clinicians from Brisbane and Sydney, and two international speakers. Feedback was extremely positive.

The study has a multi-disciplinary investigative team from the fields of medicine, physiotherapy, epidemiology, biostatistics, dietetics and occupational therapy. It has national collaborations with the Children's Hospital at Westmead, Sydney, the Royal Children's Hospital, Melbourne, the Mater Children's Hospital, Brisbane and the Royal Children's Hospital, Brisbane.

During 2012 nine articles relating to Rett syndrome were published or accepted for publication by our group. These articles included investigations of epilepsy, the phenotype of girls and women with a large deletion; the parental origin of the mutation, the course of puberty in Rett syndrome as well as an

assessment of the learning of motor skills in a conductive education setting using a single subject design study. A pilot study also examined the measurement of physical activity in Rett syndrome. Another study recruited families with a daughter with Rett syndrome in China and examined pathways to diagnosis and caring during everyday life. The journal publishing the article on pathways to diagnosis requested the same story but from an Australian perspective. This article was written by an Australian mother together with researchers on her experiences of seeking a diagnosis for her daughter and this paper was published as a companion piece to the paper on Chinese experiences.

*Funders of the project: Current: NHMRC Project Grant (1004384), NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).*

## DEVELOPING CLINICAL GUIDELINES FOR THE MANAGEMENT OF GASTRO-INTESTINAL DISORDERS AND BONE HEALTH IN PATIENTS WITH RETT SYNDROME

JENNY DOWNS, HELEN LEONARD, GORDON BAIKIE, MADHUR RAVIKUMARA, NUSRAT NASEEM, AMANDA JEFFERSON, HELEN WOODHEAD, SUE FYFE, ARIS SIAFARIKAS

Rett syndrome is frequently associated with poor growth, feeding difficulties and problems with gastro-oesophageal dysmotility such as reflux, constipation and abdominal bloating. There is limited literature on management strategies for these common gastro-intestinal conditions in Rett syndrome and we have used the Delphi technique to develop a consensus

for items that describe their assessment and management. We recruited an expert panel of clinicians and researchers who reviewed two drafts of the guidelines. We have now identified the set of recommendations for the assessment and treatment of gastro-intestinal issues, useful for clinicians who typically see only small numbers of patients with Rett syndrome. One manuscript has been submitted for publication and two manuscripts are in an advanced state of preparation.

Rett syndrome is also associated with osteoporosis and a greater likelihood of fracture in comparison with the general population. We have developed a draft set of guidelines for optimal bone health in Rett syndrome taking into account the perspectives of parents on these issues and systematic review of the literature, and have created a web-based platform for data collection from an expert panel of clinicians and researchers. We will soon finalise our expert panel for this project and commence the Delphi process to identify assessment and treatment recommendations in relation to bone health for Rett syndrome.

*Funder of the project: Rett Syndrome Association UK.*

## MULTI-REGISTRY ANALYSES OF PRE- AND PERINATAL RISK FACTORS FOR AUTISM

MICHAELINE BRESNAHAN, KIM CARTER, RICHARD FRANCIS, MIKA GISSLER, EMMA GLASSON, RAZ GROSS, NINA GUNNES, GEOFFREY HAMMOND, MADY HORNIG, CHRISTINA M HULTMAN, AMANDA LANGRIDGE, HELEN LEONARD, ANASTASIA

ILIADOU NYMAN, ERIK PARNER, MANUEL POSADA, ABRAHAM REICHENBERG, DIANA SCHENDEL, SVEN SANDIN, ANDRE SOURANDER, CAMILLA STOLTENBERG, PÅL SURÉN, EZRA SUSSER AND ANDREW WHITEHOUSE.

Population-based disease registry systems are extremely important research resources especially for conditions such as autism which are of comparatively low prevalence. Despite numerous studies investigating the association between pre- and perinatal factors and autism, many relationships remain unclear, often because sample sizes are small and methodologies vary across research groups and countries. To overcome these limitations, the International Collaboration for Autism Registry Epidemiology (iCARE) was established among researchers from Denmark, Sweden, Finland, Norway, Western Australia, Israel and the US. The aim of this initiative is to demonstrate the capabilities of a multi-national registry approach to investigate pre- and perinatal factors and autism, autism trends and variation across countries. As all sites have access to complete birth population data for their respective countries/states from which the cases of autism are ascertained, data from the multi-national registries have been used to create a common, harmonised set of variables across all sites. Using a computational infrastructure designed by the bioinformatics team at the Institute, the data, which is stored and managed at each international site, is retrieved on demand and pooled to create a virtual dataset. Analysing this dataset allows us to use the power of data from all countries/states to investigate the relationships between pre and perinatal factors and autism. This virtual dataset also allows cross-country comparisons, and ensures that

common methodologies are used. There are several papers currently being prepared for publication.

Mid year 2012 the group was awarded NIH Autism Centers of Excellence funding under the leadership of Abraham Reichenberg, from the Mount Sinai School of Medicine, New York. The aim of this new network will be to examine fundamental controversies concerning familial and environmental contributions to risk for autism spectrum disorders. We will investigate familial and pregnancy-related environmental factors and assess the transmission of risk across generations including the potential mediating role of epigenetic mechanisms. To achieve this we will build on the existing population-based epidemiologic resources from the seven countries and archived biospecimens from some of these countries. The combined data will be based on over 4.5 million births (1998-2007), over 20,000 cases of ASD, and family-linked data over three generations including genetically-informative family relations (parents, grandparents, aunts, uncles, cousins, full and half siblings).

*Funders of the project: Autism Speaks. National Institutes of Health*

## THE NATURAL HISTORY OF THE CDKL5 DISORDER: DEVELOPMENT OF AN INTERNATIONAL REGISTER

STEPHANIE FEHR, HELEN LEONARD, JOHN CHRISTODOULOU, MEREDITH WILSON, ALISON ANDERSON, AMI BEBBINGTON, SIMON WILLIAMS AND JENNY DOWNS

The CDKL5 disorder, which is caused by mutations in the *cyclin-dependent kinase-like*

5 (*CDKL5*) gene, is a newly identified cause of early-onset seizures and gross motor and intellectual impairment. In the past some children and adults with mutations in the *CDKL5* gene may have been diagnosed with atypical Rett syndrome or infantile spasms. In 2011, however, we studied questionnaire and genetic data from 86 families living in 14 different countries (majority being USA and UK) who were participating in our InterRett Database. We found that only a minority of children and adults with the *CDKL5* disorder actually met the clinical criteria for Rett syndrome. We therefore suggest that the *CDKL5* disorder is an independent clinical entity. Examination of photographs of 67 children by clinical geneticist/dysmorphologist Dr Meredith Wilson, also confirmed that these children shared similar features of the face and hands. In conjunction with Professor John Christodoulou from the Children's Hospital Westmead and a number of international clinicians, this work was published this year in the European Journal of Human Genetics.

Since 2011 we have been collaborating with the International Foundation for *CDKL5* Research to establish a new international *CDKL5* disorder register using our InterRett database and study processes as a model. This register aims to collect information on additional cases with the *CDKL5* disorder from families and their clinicians to increase the precision of our description and to describe the natural history of the disorder. As part of this study, a consumer reference group was established comprising mothers of a child with the *CDKL5* disorder from the USA, UK, Australia and the Netherlands. Further to development of the questionnaire and with considerable input from this reference group

recruitment for the new register commenced in October 2012. The questionnaire is available in online and paper formats and translations into other languages are planned with a Spanish translation commencing in 2012. By year end 136 families had been recruited and 24 had already completed the questionnaire with a further 35 in progress. Data collection will continue in 2013. We have also established links with Dr Tim Benke in Colorado who has a special interest in childhood epilepsy to forward the development of a clinician questionnaire specific to the *CDKL5* disorder.

*Funders of the project: International Rett Syndrome Foundation, International CDKL5 Foundation.*

## DETERMINANTS AND OUTCOMES OF PRETERM BIRTH & PATHWAYS INTO DEVELOPMENTAL DISORDERS

FIONA STANLEY, HELEN LEONARD, GEOFF HAMMOND, AMANDA LANGRIDGE, KRISTJANA EINARSDOTTIR, AMI BEBBINGTON, JENNY BOURKE, NICK DE KLERK, PETER JACOBY, STEVE BALL, GAVIN PEREIRA, EVE BLAIR

Increases in preterm birth and survival over time of those born pre-term are occurring due to a range of factors. These include increasing maternal age and co-morbidity (particularly obesity and maternal diabetes), increases in multiple births, social factors such as higher fertility rates in socially disadvantaged high risk mothers and changes in obstetric practice relating to reproductive technologies, early induction of labour and use of caesarean section. Our group undertakes complex statistical analyses principally using linked

deidentified Western Australian population data relating to pregnancies, births and hospitalisations to investigate the determinants and outcomes of preterm birth and the pathways leading to developmental disorders. We have already shown how the determinants of both spontaneous and medically indicated pre-term births are changing over calendar time. We have also compared neonatal outcomes for babies born pre-term in the public and private systems. Interestingly following the Australian Private Health Insurance Incentive policy reforms, which were implemented in 1997–2000, births in privately insured patients and also caesarean deliveries increased. Our current work also includes investigations of the relationship between various environmental and geographic factors and pregnancy complications and birth outcomes.

Further to our examination of the causes of pre-term birth, the next step will be to follow these vulnerable infants born at different gestational ages and determine what factors increase or decrease their likelihood of survival with or without a major developmental disability (e.g. intellectual disability, cerebral palsy and autism). This will allow us to explore the impact of changes in antenatal and perinatal care on these important pathways. As well as measuring the contribution of preterm birth to developmental disabilities, we also plan to measure the later hospitalisation experience of children born at different gestational ages and with different developmental disabilities. This will provide the basis for economic analyses of the costs associated with preterm birth and with specific developmental disabilities.

*Funders of the project: NHMRC Program Grant*

(572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

## IDEA - INTELLECTUAL DISABILITY EXPLORING ANSWERS

CAROL BOWER, HELEN LEONARD, JENNY BOURKE, AMI BEBBINGTON, PATRICK FITZGERALD, AMANDA LANGRIDGE, GEOFF HAMMOND

The IDEA Database provides an infrastructure for population-based epidemiological research into the causes and prevention of intellectual disability as well as the outcomes for those affected. Information in the database is sourced from data from the Disability Services Commission (DSC) since 1953, as well as information from the Department of Education for children born since 1983. IDEA is currently being updated with notifications of children identified with an intellectual disability from the Department of Education and the Disability Services Commission to the end of 2010. These records are linked by the Western Australian Data Linkage Unit (DLU) to each other and to all current notifications on the database in order to minimise any duplications. Medical information on cause of intellectual disability is provided from Disability Services Commission.

Current prevalence rates for intellectual disability calculated on the WA births from 1983-2003 and ascertained up to 2008 gives a rate of 17.6/1000 livebirths. This is an increase on the previous prevalence rate of 14.3/1000 livebirths, calculated using births from 1983-1992 and ascertained up to 1999. Whilst more recent data to 2010 will be analysed in 2013, data to 2008 suggest that the prevalence of mild-moderate

intellectual disability may have increased among children born in the nineties. This will be further investigated to try to identify the reason for this rise and whether it might relate to an increase in the diagnosis of autism spectrum disorders or another cause.

Recent articles published in the scientific literature using data from the IDEA database have investigated the relationship between heavy alcohol consumption during pregnancy and intellectual disability in the offspring; maternal conditions and perinatal factors associated with intellectual disability and autism; and hospitalizations in children with intellectual disability and autism. This third study showed an increased risk of hospitalisation in childhood which varied from 2 to 10 times that of the rest of the population- an important finding which can inform service planning or resource allocation for these children with special needs.

Investigations currently underway include: the pattern of hospitalisations for children with Down syndrome; the causes of hospitalisation for children with intellectual disability and autism; exploring the pathways to contact with Juvenile Justice for Aboriginal children in order to support a strategy for change; and the co-occurrence of intellectual disability and autism within families. A book chapter for the International Review of Research in Developmental Disabilities is also being prepared which will outline linked data studies in WA which have utilised the IDEA Database.

The IDEA Database is overseen by the IDEA Advisory Council. The current members are Professor Carol Bower (Chair), Dr Helen Leonard, Jenny Bourke, (TICHR), Dr Vera Morgan (UWA),

Richard Sanders (Department of Education), Robyn Cooksey (Department of Education), Kerry Stopher (DSC), Nick Cantatore (DSC), Dr Peter Rowe (State Child Development Centre) and Charlie Rook (Consumer).

*Funders of the project: Disability Services Commission.*

## THE TRANSITION FROM SECONDARY SCHOOL TO ADULTHOOD: EXPERIENCES AND LIFE OUTCOMES FOR YOUTH WITH AN INTELLECTUAL DISABILITY AND THEIR FAMILIES

HELEN LEONARD, CAROL BOWER, NICK DE KLERK, GWYNNYTH LLEWELLYN, STEWART EINFELD, TREVOR PARMENTER, VIVIENNE RICHES, BRUCE TONGE, NICK LENNOX, RON CHALMERS, JOHN BRIGG, GREG LEWIS, JACKIE SOFTLY, JENNY BOURKE, PAULA DYKE, KITTY FOLEY, KATHERINE BATHGATE, TERRI PIKORA, SONYA GIRDLER, LYN MCPHERSON.

This ARC Linkage project, which developed from an ARACY Seed-funding grant, seeks to explore the challenges faced and outcomes achieved by young people with an intellectual disability as they move from secondary school into adult life. There are likely to be major life changes for these young people as they move into adulthood with respect to work, where they live, who cares for them, how their health and therapy needs are managed and how they spend their days. The study is investigating the factors at an individual, educational, family, and societal level which contribute positively and negatively to a 'good' outcome for the young person and their family.

This study involves young people with

intellectual disability aged 16 years and over from four separate sources: i) Down syndrome NOW cohort in WA, (ii) the Queensland Centre for Intellectual and Developmental Disability's ASK study (a five year project aiming to improve the health of young people with intellectual disability by implementing and evaluating the effectiveness of a combined education and health intervention package); (iii) the Australian Child to Adult Development Study at the University of Sydney and (iv) the Australia-wide Rett syndrome cohort. We used the World Health Organization's *International Classification of Functioning, Disability and Health* (ICF) framework to take into account the many issues which may affect a person's participation in all aspects of life. Environmental factors, which include family characteristics such as income, availability of transport, parental health and family functioning, as well as the health of the young person and their individual level of functioning, may all contribute to the young person's participation in society.

In 2009/10 questionnaires were administered to 269 families of young people with Down syndrome in Western Australia. Of the 203 (75.0%) returned, 164 (80.8%) had left school with ages varying from pre-transition (16-17 years), early transition (18-20 years) to late transition (23-31 years). Follow-up questionnaires were administered in 2011/2012 to 229 families with 197(86%) families responding.

In consultation with the WA research team the Queensland group administered a similar questionnaire to the parents of the young people, aged between 17 and 23 years, in the Queensland ASK cohort, with 150 (59%)

respondents. Using the existing ACAD data previously collected in New South Wales and Victoria we hope to compare the effects of legislative and policy differences on employment options between states.

Based on the 2009 Down Syndrome NOW data, among those who had left school (n=164) the most common main day occupation was sheltered employment (39.0%), followed by open employment (25.6%) and alternatives to employment (ATE) (25.0%) while the remainder (10.4%) attended training. Not unexpectedly young adults who were reported as functioning better within self-care, community and communication skills were more likely to be participating in open employment or training than those in sheltered employment or alternatives to employment. However we did not find any evidence that poor health status adversely impacted on workplace participation. Similarly, families of young people with Down syndrome attending open employment reported better quality of life than families of young people attending sheltered employment. The young person's behaviour had a weak association with family quality of life.

We also conducted a qualitative study to investigate the experiences of mothers of young adults with either Down syndrome or Rett syndrome who were transitioning from secondary school to adult life. In contrast with Rett syndrome, mothers of young adults with Down syndrome described more difficult pathways to attaining stability in adult roles. The facilitators and barriers which emerged were in the area of support, relationships, services, systems and policies. The study highlighted the unwavering commitment of parents to their

son or daughter with an intellectual disability and the extraordinary resourcefulness of many families in their quest to ensure that their son's or daughter's quality of life is maximised.

Further analysis will explore the changes in behavior of young people with Down syndrome over time and its relationship with their post-school activities. These data will also be explored to identify issues related to accommodation and respite needs among this group.

A lay summary booklet of the findings of previous Down syndrome research undertaken within the group has been published and distributed to all families who have participated in current and previous Down syndrome studies. A copy of the report is available on the website at <http://www.childhealthresearch.org.au/our-research/projects-index/d/down-syndrome.aspx>

## WA REGISTER FOR AUTISM SPECTRUM DISORDERS

EMMA GLASSON, KATHERINE RUSSELL-SMITH, AINSLEY READ, CAROL BOWER.

The aim of the WA Register for Autism Spectrum Disorders is to monitor diagnostic trends of conditions characterized by autism (autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)). These disorders develop in young children and have significant life-long effects in the areas of social interaction, communication and behaviour. The WA Autism Register is ongoing and between 1999 and 2012 information has been collected on more than 4,000 individuals.

*Funder of the project:*

*Government of Western Australia, Department of Health:*

## WESTERN AUSTRALIAN AUTISM BIOLOGICAL REGISTRY

ANDREW WHITEHOUSE, JOHN WRAY, DAVID RAVINE, ANNA HUNT, RACHEL JONES

The aim of the **Western Australian Autism Biological Registry (WAABR)** is to collect detailed information on children with autism in WA and their families and to centralize this information so that it is accessible to those who are involved in autism research. The study has three components to allow us to obtain the best information about the child with autism. These are questionnaires, clinical assessment and blood samples of the child and parents. The WA Autism Biological Registry began its recruitment in early 2012, with our first participant coming through the doors in March 2011. By the end of 2012, we had seen our 200th participant. This makes WAABR the largest biobank of autism information in the southern hemisphere. Our aim is to reach 500 families within the next two years.

*Funders of the project: National Health & Medical Research Council*

## THE FLUOXETINE FOR AUTISTIC BEHAVIOURS TRIAL

ANDREW WHITEHOUSE, JOHN WRAY, JO GRANICH, DINAH REDDHOUGH, CATHERINE MARRAFFA, PHILIP HAZELL, DAVID DOSSETOR

Repetitive behaviours (RBs) constitute one of the three core impairments that affect children and adolescents with an autism spectrum disorder

(ASD). These behaviours are typically initiated and exacerbated by associated anxieties that can significantly impact upon daily life. The Fluoxetine for Autistic Behaviours (The FAB Trial) is a multi-site randomized controlled trial seeking to investigate the use of Fluoxetine (anti-depressant medication also known as Prozac) for the treatment of RBs for the first time in Australia. Lack of gold standard evidence for the effectiveness, optimal dosing and safety of Fluoxetine has meant that this medication is commonly used "off the label" as treatment for RBs and anxieties among the paediatric population living with ASD. The recruitment for eligible participants (aged 8-17 years) across all sites (WA, NSW and Victoria) has been wide-spread and continuing with over 60 children participating in this trial to date.

The findings of this trial will provide evidence-based information for individuals with ASD and their families. The research outcomes will enable families to make better informed decisions about placing their child on this medication as a way of managing their symptoms of ASD. Similarly, the results will inform physicians and provide sound clinical guidelines and practice related to the use of Fluoxetine and its appropriateness for RBs including the plausible side-effects of this medication for this population. The FAB trial is expected to finish in 2013.

*Funders of the project: National Health and Medical Research Council*

## PREGNANCY INVESTIGATION OF SIBLINGS AND MOTHERS OF CHILDREN WITH AUTISM (PRISM)

ANDREW WHITEHOUSE, MURRAY MAYBERY, CHERYL DISSANAYAKE, MARTHA HICKEY, CRAIG PENNELL, JO GRANICH, ANNA HUNT, LISA UNWIN.

Studying fetuses 'at risk' for autism is the aim of a world-first longitudinal research study named **PR**egnancy **I**nvestigation of **S**iblings and **M**others of children with autism (**PRISM**). This NHMRC funded study is seeking to investigate specific *in-utero* bio-markers for autism by looking at aspects of fetal development, such as fetal brain growth and the prenatal hormone environment. State-of-the-art ultrasound technology used at three gestational time points (18, 24, and 28 weeks) is enabling this aspect of pregnancy to be examined among two groups of women. Pregnant mothers with subsequent pregnancies who have an existing child with autism (cases) are compared with mothers who have a child with neuro-typical development (controls). Newborns umbilical cord blood is collected to further study the DNA and examine their exposure to pregnancy hormones. Children's growth and development is monitored via standard measures and direct observations at four time points until their second birthday.

Over 50 women are now participating in this research across both arms of the study. By the end of 2015, we aim to recruit over 100 pregnant mothers. The findings of this research may provide insight into the early onset and atypical development of fetal brain growth. In addition, the study outcomes may lead to a breakthrough in identifying specific biological risk factors for autism early in life. This may have

implications for the development of preventative *in-utero* measures. Collectively, the results of this study will bear significant implications on early diagnosis of autism and possible commencement of early intervention therapies for the treatment of autism among much younger children than ever before. Overall, the PRISM findings are likely to have enormous impact on the future outcomes of young children affected by autism and their families.

*Funders of the project: National Health and Medical Research Council*

### WA CEREBRAL PALSY STUDIES

EVE BLAIR, LINDA WATSON, FIONA STANLEY, CAROL BOWER

Cerebral palsy (CP) is an umbrella term covering chronic neurological conditions affecting movement and posture, ranging in severity from barely noticeable to severely disabling. The primary pathology lies in the brain, but for most the cause is poorly understood. CP results in life-long disability, and since there is as yet no cure, prevention and effective management are top priorities.

### THE WA REGISTER OF DEVELOPMENTAL ANOMALIES - CEREBRAL PALSY

LINDA WATSON, EVE BLAIR, FIONA STANLEY, CAROL BOWER

Statutory notification of CP and birth defects was introduced in WA in January 2011, with the CP and Birth Defects Registers combining under the name of the WA Register of Developmental Anomalies (WARDA). The WA CP Register is now

known as WARDA – CP.

WARDA - CP, which has existed continuously since 1979, is used to monitor the occurrence of CP in WA, carry out research to investigate its causes and evaluate treatment strategies, identify CP as a long-term outcome in other WA studies and assist in the planning of services for people with CP. A birth cohort is included in analyses after case data are updated at age 5 years; the register is now considered complete to 2007.

WARDA - CP is also responsible for contributing data to the Australian CP Register (ACPR), a national collaboration initiated by the WA team in 2002 to provide information about CP throughout Australia and create a larger study population to enable more effective research. The administrative centre relocated in 2007 to the Research Institute of the CP Alliance in NSW where it continues to flourish. The first report of the ACPR was published in 2009, and the second is in preparation.

*Funders of the project:*

*WARDA - CP is presently funded by NHMRC Program Grant #572742 Early developmental pathways linking health, disability, education, welfare and justice (2010-2014).*

### DEVELOPING A RELIABLE SYSTEM OF DESCRIBING CP

SARAH LOVE, NOULA GIBSON, EVE BLAIR, LINDA WATSON

The cerebral palsies include a wide range of motor impairments across the spectrum of severities and may be accompanied by a wide variety of other impairments which can greatly affect both functionality and treatment options. The validity of generalising the results of research depends heavily on a consensus understanding of what segment of the CP population the research refers to. International attention has been focused on the challenge of standardising the classification of CP for several decades, during which time WA has been at the forefront of promoting description rather than classification and developing a reliable

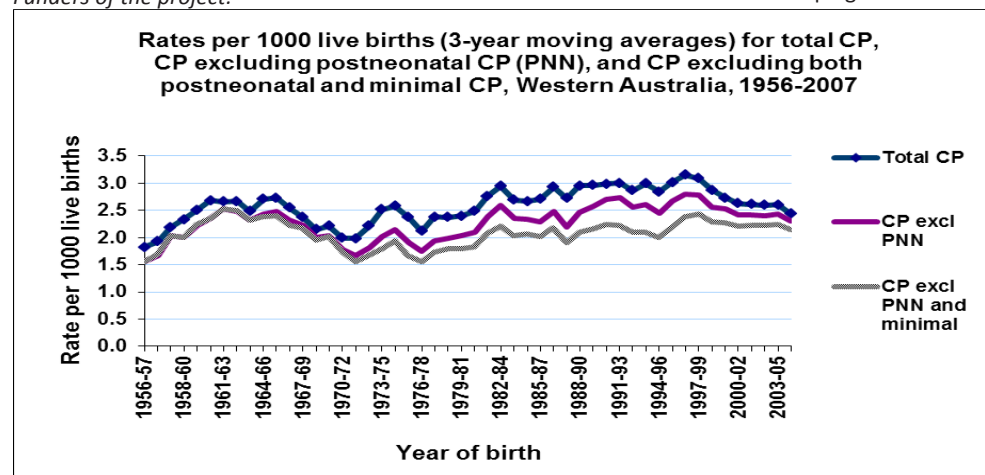
system of describing the clinical features of CP. We are continuing to develop and promote an innovative diagrammatic limb-by-limb CP Description Form which incorporates the Australian Spasticity Assessment Scale (ASAS) devised by Sarah Love and Noula Gibson, Cerebral Palsy Habilitation Physiotherapists, who have led this work. A booklet defining every aspect of the CP Description Form and a Training and Reference video demonstrating the use of the ASAS and showing examples of the different forms of CP are both nearing completion.

*Funders of the project: PLAN Australia generously funded the development of the ASAS, the CP Description Form and the Training and Reference DVD. A PMH Foundation Special Project Grant 2007 has covered travel to conduct training sessions throughout WA, and an Innovative Research Grant from the CP Institute has funded the extension of training across Australia.*

### CASE CONTROL STUDIES OF CP IN TERM AND PRETERM INFANTS IN WA, 1980 TO 1995

EVE BLAIR, SARAH MCINTYRE, LINDA WATSON, NADIA BADAWI, KARIN NELSON

Comprehensive maternal, birth and neonatal information on CP cases, matched controls, and a sample of unexplained perinatal deaths born 1980-1995 was collected from birth hospitals throughout the State. This has provided a wealth of data from which to identify causal pathways to the different outcomes. The primary aim of these studies is to prevent the occurrence of brain damage responsible for CP by identifying points on each causal pathway to



CP at which it may most effectively, efficiently and ethically be interrupted. Data analysis continues with the intent to explore causal pathways and report research findings at local, national and international forums.

The current focus of our analyses is on singleton births occurring after 35 completed weeks of gestation (term and late preterm singletons). This relatively low risk group has received little research attention, yet it comprises 30% of all perinatal deaths and 70% of all CP and is very likely to be the most aetiologically heterogeneous. In an effort to create more aetiologically homogeneous groups we have identified subjects with abnormal neonatal neurological signs and the subset of this group whose signs were attributed to acute intrapartum hypoxia. We have identified that 53% of neonatal deaths and 68% of CP in our sample did not appear neurologically abnormal in the neonatal period. The antecedent factors of all outcomes are being compared.

*Funders of the project: This case-control study was funded by NHMRC Program Grants #353514 (2005-2009) and #572742 (2010-2014). An Innovative Research Grant from the CP Institute provides additional funds for analysis and travel.*

## Childhood Cancer

### AUSTRALIAN STUDY OF CAUSES OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN

ELIZABETH MILNE, CAROL BOWER, NICK DE KLERK, URSULA KEES, IN COLLABORATION WITH BRUCE ARMSTRONG, FRANK VAN BOCKXMEER, MICHELLE HABER, RODNEY SCOTT, JOHN ATTIA,

MURRAY NORRIS, LIN FRITSCHI, MARGARET MILLER, JUDITH THOMPSON, FRANK ALVARO, CATHERINE COLE, LUCIANO DALLA POZZA, JOHN DAUBENTON, PETER DOWNIE, MARIE KIRBY, LIANE LOCKWOOD, GLENN MARSHALL, ELIZABETH SMIBERT, RAM SUPPIAH .

Researchers in the Childhood Cancer Epidemiology program have been analysing the data collected between 2003 and 2007 in this national case-control study of the causes of childhood acute lymphoblastic leukaemia (ALL). The primary hypothesis of this study was that maternal folate supplementation during pregnancy protects against ALL in the offspring, with the effect modified by genetic factors in folate metabolism.

The following papers were published in 2012:

Cooper MN, de Klerk NH, Greenop KR, Jamieson S, van Bockxmeer F, Anderson D, Armstrong BK, Milne E. Statistical correction of genotyping error in a case-control study of childhood leukaemia. *BMC Research Methods*. 2012; 12. doi:10.1186/1471-2288-12-141

This paper describes the development and application of a novel statistical adjustment method for use in the correction of genotyping error.

Bailey HD, Miller M, Langridge A, de Klerk NH, van Bockxmeer FM, Attia J, Scott RJ, Armstrong BK, Milne E. Maternal dietary intake of folate and vitamins b6 and B12 during pregnancy and the risk of childhood acute lymphoblastic leukemia. *Nutr. Cancer* 2012;64:1122-30.

In this paper, we present our findings of a modest protective effect of higher maternal dietary intake of folate and vitamin B12 during pregnancy against ALL in the offspring, more

particularly among women who drank alcohol during pregnancy.

D Glass, A Reid, H D Bailey, E Milne, L Fritschi. Risk of childhood acute lymphoblastic leukaemia following parental occupational exposure to pesticides. *Occupational and environmental Medicine*. 2012; 69:846-9.

This paper reported that paternal occupational exposure to pesticides before or around conception was not related to increased risk of childhood ALL.

Orsi L, Rudant J, Bonaventure A, Goujon-Bellec S, Corda E, Evans TJ, Petit A, Bertrand Y, Nelken B, Robert A, Michel G, Sirvent N, Chastagner P, Ducassou S, Rialland X, Hémon D, Milne E, Scott RJ, Baruchel A, and Clavel J. Genetic polymorphisms and childhood acute lymphoblastic leukemia: GWAS of the ESCALE study (SFCE) *Leukemia*. 2012, June 4.

This paper describes novel findings from a GWAS of children with ALL in France, and compares them with findings from Aus-ALL.

Analysis is also under way to examine whether there are links between risk of ALL and:

- the types of jobs parents had
- variations in genes that influence the way the body processes food and chemicals
- medication use before/during pregnancy and by the child

*Funders of the project: NHMRC Grant #254539, and Cancer Council WA.*

### NATIONAL CASE-CONTROL STUDY OF THE CAUSES OF CHILDHOOD BRAIN TUMOURS

ELIZABETH MILNE, CAROL BOWER, NICK DE KLERK, PETER DALLAS, IN COLLABORATION WITH BRUCE ARMSTRONG, FRANK VAN BOCKXMEER, RODNEY SCOTT, JOHN ATTIA, LIN FRITSCHI, DAVID ASHLEY, LESLEY ASHTON, JUDITH THOMPSON, MURRAY NORRIS, RICHARD COHN, MARGARET MILLER, LUCE DALLA POZZA, JOHN DAUBENTON, TIMOTHY HASSALL, MARIA KIRBY, STEWART KELLIE, ROSS PINKERTON, FRANK ALVARO, ANGELA ALESSANDRI.

The Australian Study of Childhood Brain Tumours (AUS-CBT) was a national case-control study into the causes of childhood brain tumours (CBT). It aimed to investigate genetic, dietary and environmental risk factors for CBT, and is the sister study to the Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (AUS-ALL). The study recruited case and control families between 2006 and 2010; data collection was completed in 2011.

The study involved children aged 0-14 years. Case children and their parents were recruited from the nine paediatric oncology units nationwide. In total, we were notified of 734 eligible cases, of whom 568 were invited (77%) to participate and 374 consented, with 335 providing either self-administered questionnaires or doing short telephone interviews to provide demographic and basic exposure data. 302 case families returned full exposure questionnaires, and 295 did a food frequency questionnaire. We received DNA samples from 355 families for genotyping, which is complete. A total of 194 families declined to participate or could not be re-contacted, and a

further 162 were not invited due to medical or psychosocial reasons.

Control children (that is, children without a brain tumour) and their families were recruited through national random digit dialling and frequency matched to the case children by age, sex and State of residence. A total of 1363 controls were recruited. We received exposure questionnaires from 941 control families, food frequency questionnaires from 726 control families and DNA samples from 974 control families for genotyping, which is complete.

The following papers were published in 2012:

Milne E, Greenop KR, Bower CI, Miller M, van Bockxmeer FM, Scott RJ, de Klerk NH, Ashton L, Gottardo NG, Armstrong BK. Maternal use of folic acid and other supplements and risk of childhood brain tumors *Cancer Epidemiology, Biomarkers and Prevention*. 2012; 21(11):1-9.

In this paper, we present results suggesting that maternal use of folic acid supplements before and possibly during pregnancy may protect against childhood brain tumours

M Mazloum, HD Bailey, T Heiden, BK Armstrong, N de Klerk, E Milne. Participation in population-based case-control studies: does the observed decline vary by socio-economic status? *Paediatric and Perinatal Epidemiology*. 2012; 26:276-9.

In this paper we compared the socioeconomic status of recruited controls in the Aus-ALL study and the Aus-CBT study. We found that participation rates were lower in Aus-CBT than Aus-ALL, and that controls from both studies had higher socioeconomic status than that of the general population, but were quite similar to

each other.

Analysis and manuscript preparation are under way to examine whether there are links between risk of CBT and:

- Exposure to paints and pesticides at home
- Variations in genes that influence the way the body processes food and chemicals

*Funders of the project: NHMRC Grant #404089.*

## NUTRITION AND GENOME HEALTH IN CHILDREN

ELIZABETH MILNE, MICHAEL FENECH, BRUCE ARMSTRONG, NICK DE KLERK, MARGARET MILLER

The Nutrition and Genome Health in Children Study aimed to identify key nutritional and genetic factors associated with DNA damage in children. It aimed to describe the nature of the interaction between nutritional and genetic factors in determining level of DNA damage in children, and also the associations between body mass index, DNA damage and micronutrient levels in children.

This study was a cross-sectional study of 450 Western Australian children, conducted between 2009 and 2011. Participants were children aged 3, 6 or 9 years at recruitment who had never been diagnosed with asthma, diabetes, cancer, arthritis or epilepsy. Participants and their parents were recruited via primary schools, posters displays and flyers, advertisements in local newspapers and information letters distributed to a wide range of organisations. These include crèches, day care centres, playgroups, sports centres and libraries.

The child's diet and macro- and micro-nutrient intake was assessed using parent-completed Food Frequency Questionnaires (FFQs). A sample of the child's blood was taken and used to assess micronutrient levels and specific biomarkers of DNA damage. The blood sample was also used to identify genetic polymorphisms related to nutrient metabolism and DNA repair. Saliva samples collected from the child were used to measure cortisol and cotinine levels, as indicators of psychological stress and exposure to environmental tobacco smoke, respectively. Parents were given feedback on their child's diet, and dietary advice was provided by a dietician where needed.

In all, 464 participants provided data. Statistical analysis of these data is currently in progress.

*Funders of the project: NHMRC Grant#572623*

## Infectious Diseases

### MONITORING CARRIAGE OF STREPTOCOCCUS PNEUMONIAE AMONG ABORIGINAL CHILDREN AND ADULTS IN WESTERN AUSTRALIA STAFF AND STUDENTS

DEBORAH LEHMANN, ANKE HOSKINS, DEIRDRE COLLINS, JANICE LIM, KALPANI SENASINGHE IN COLLABORATION WITH JACINTA BOWMAN, NATALIE THOMSEN, TOM RILEY, CAROLIEN GIELE, PAUL EFFLER, AMANDA LEACH, PETER RICHMOND

*Streptococcus pneumoniae* (pneumococcus) can cause middle ear infections and invasive pneumococcal disease (IPD) resulting in meningitis, pneumonia and septicaemia (blood poisoning). The Australian Aboriginal population

has among the highest reported IPD rates worldwide. The existence of over 90 known types (serotypes) of pneumococci increases the challenge of prevention. A pneumococcal conjugate vaccine (Prevenar-7™, PCV7) covering the 7 most common serotypes causing IPD in a 2-4-6-month schedule and an 18-month booster with a pneumococcal polysaccharide vaccine (Pneumovax™) covering 23 serotypes have been offered to Aboriginal children since 2001. Pneumovax™ is also offered to adults. While there has been a marked reduction in IPD due to the near elimination of Prevenar-7™ serotypes, there has been an increase in IPD rates, particularly in young Aboriginal adults, due to serotypes not included in the vaccine. In light of this, Prevenar-7™ was replaced with Prevenar-13™ on 1 July 2011, which covers 6 additional serotypes.

Pneumococci are carried in the back of the nose of healthy as well as sick individuals and the acquisition of pneumococci is prerequisite to develop disease. Surveillance of pneumococcal carriage offers important complementary information to data on IPD since it can quickly provide a large amount of information on serotypes circulating in the population. It also gives a conservative estimate of antibiotic resistance of invasive pneumococcal strains.

This study aims to monitor the impact of different versions of PCV on pneumococcal carriage by collecting pernasal swabs opportunistically from Aboriginal adults and children in urban, rural and remote areas of Western Australia. We also collect ear swabs from children with middle ear discharge and data on vaccination status of children in the study.



Other study aims include:

1. Describing the prevalence of upper respiratory tract (URT) carriage of other pathogens identified on primary culture
2. Comparing the distribution of pneumococcal serotypes in the URT with those causing IPD in Aboriginal adults and children annually
3. Monitoring antibiotic resistance pattern of pneumococci
4. Storing pernasal swabs for detection of viruses by PCR to describe the prevalence of respiratory viruses and
5. Investigating viral-bacterial interactions in the URT.

To date we have collected ~2200 pernasal swabs and 50 swabs of discharge from the middle ear.

Pneumococcal carriage rates remain high in young children, being highest in the 6-23 month age group (~80%). Approximately 12% of young adults and 10% of people over 65 years of age carried pneumococci. In children under 5 years of age nontypeable *Haemophilus influenzae* was grown from 62% and *Moraxella catarrhalis* from 68% of pernasal swabs. In people aged ≥5 years 22% grew nontypeable *Haemophilus influenzae* and 27% grew *Moraxella catarrhalis*. Thirty four different pneumococcal serotypes were carried in children <5 years of age and 37 different serotypes have been identified in people ≥5 years. Currently, the most common pneumococcal serotypes in children <5 years of age are 19F, 6C and 16F while 19F, 6A/6C and 10A are most common in older children and adults. There has been some reduction in carriage of serotypes included Prevenar-13™

since its introduction 18 months ago but the proportion of serotypes identified in the URT which are not covered by Prevenar-13™ remains high (~70%). Surveillance is ongoing.

Our findings were presented at the 8th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD8) in March 2012. A manuscript describing URT carriage until July 2011 is in advanced draft stage.

*Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation (CARE) and NHMRC Project Grant #545232 (a collaboration with the Menzies School of Health Research)*

## AETIOLOGY, BURDEN AND CAUSAL PATHWAYS OF ACUTE LOWER RESPIRATORY INFECTIONS USING POPULATION LINKED DATA

HANNAH MOORE, DEBORAH LEHMANN, KHADRA JAMA-ALOL, PETER JACOBY, NICHOLAS DE KLERK IN COLLABORATION WITH PETER RICHMOND, DAVID SMITH, ANTHONY KEIL, CHRISTOPHER BLYTH.

Acute lower respiratory infections (ALRI), or chest infections like influenza and pneumonia, are a major cause of illness in young children. The primary objective of this project is to describe the aetiology, burden and causal pathways of ALRI in Aboriginal and non-Aboriginal children from a 10-year birth cohort (245, 249 births) using population linked data from the Western Australian Data Linkage System. Datasets include the Midwives' Notification System, Hospital Morbidity Database System, Birth and Death Register, Emergency Department Data Collection,

Birth Defects Register and the PathWest Laboratory Database. This project is the first to link statewide laboratory data for respiratory pathogens to other datasets within the Western Australian Data Linkage System.

A manuscript describing metropolitan emergency department presentations for respiratory infections has been submitted for publication. A second manuscript investigating the risk of ALRI in children with birth defects is in advanced draft stage. The key findings of this project are:

- Hospitalisations for all-cause pneumonia in Aboriginal children fell by 28-44% in 2001-2005 compared to 1996-2000.
- The gap in the burden of ALRI between Aboriginal and non-Aboriginal children fell by a third.
- Male gender, being born in autumn and multiple pregnancies are risk factors for hospitalisation for ALRI in both Aboriginal and non-Aboriginal children <2 years.
- Children born by elective caesarean are at increased risk of hospitalisation for bronchiolitis.
- Respiratory syncytial virus (RSV) was the most commonly identified respiratory pathogen, identified in >39% of hospitalizations.
- Children born with birth defects are at greater risk of hospitalisation for ALRI before age 2 years than children without birth defects.
- Some pathogens could be identified across a range of diagnosis codes, indicating

that reliance on diagnostic codes could underestimate the true burden of pathogen-specific ALRI.

- Seasonality for bronchiolitis and RSV-related hospitalisations varies between different health regions in WA and as such, localized immunoprophylaxis schedules are required.

*Funders of the project: NHMRC Project Grant #572590*

## HOSPITALISATION FOR DIARRHOEA AMONG WESTERN AUSTRALIAN CHILDREN

DEBORAH LEHMANN, HANNAH MOORE, FAYE LIM IN COLLABORATION WITH KARTHIK MANOHARAN, GEOFF SHELLAM.

Diarrhoea is a significant reason for hospitalisation in Australian children. This study utilising total population-based data from the Maternal and Child Health Research Database investigates the trends in hospital admissions for diarrhoeal diseases (gastroenteritis) in Western Australian children aged <15 years between 1983 and 2006. Hospitalisation rates for gastroenteritis are highest in children aged 6-11 months. Over the last two decades, we have seen diverging trends in hospitalisations for gastroenteritis between Aboriginal and non-Aboriginal children. In Aboriginal children aged 6-11 months, rates have fallen from 304 per 1000 population/annum in 1983-1994 to 214/1000 in 1995-2006 with similar trends in other age groups. In non-Aboriginal children, hospitalisation rates for gastroenteritis have increased from 1987 to 1999 and then declined from 2001 to 2006 when they were

approximately 20/1000 in those aged 6-11 months. Trends in gastroenteritis hospitalisation rates varied between geographical regions of the state. This study provides important baseline data on hospitalisations for diarrhoeal disease for evaluation of the rotavirus vaccination program introduced in 2007. A manuscript reporting our findings has been submitted for publication.

*Funders of the project: NHMRC Program Grant #353514*

## INVESTIGATING THE RISK FACTORS AND CO-MORBIDITIES ASSOCIATED WITH INVASIVE PNEUMOCOCCAL DISEASE IN THE WESTERN AUSTRALIAN POPULATION

DEBORAH LEHMANN, FAYE LIM, HANNAH MOORE, CATHERINE HARRISON, JUDITH WILLIS IN COLLABORATION WITH AOIFFE MCLOUGHLIN, CAROLIEN GIELE AND ANTHONY KEIL.

The Vaccine Impact Surveillance Network (VISN) conducted enhanced surveillance on Invasive Pneumococcal Disease (IPD) between 1996 and 2007. Everyone is susceptible to IPD, though most at risk are children under the age of 2 years, elderly persons and those with chronic disease and compromised immune systems. The Australian Aboriginal population has among the highest reported IPD rates worldwide and incidence rates in this population are higher across all age groups than in non-Aboriginal people. Since January 2008, the Communicable Diseases Control Directorate (CDCD) has conducted the surveillance of IPD across Western Australia. Our previous publications reported on the incidence and serotype

distribution of IPD notifications in the WA Aboriginal and non-Aboriginal population. This project involves analysis of the IPD surveillance data between 1997 and 2007 to investigate the underlying co-morbidities and risk factors associated with IPD. We aim to describe the co-morbidities reported in IPD cases according to age, gender, geographical region and Aboriginal status. Major findings to date are:

- Approximately 64% of IPD cases occurred in adults aged  $\geq 15$  years.
- Cardiovascular disease and chronic respiratory disease were the most common co-morbidities in non-Aboriginal adults aged  $\geq 15$  years.
- Smoking and excessive alcohol uses were the most common risk factors in Aboriginal adults aged  $\geq 15$  years.
- Smoking was the most common risk factor in Aboriginal and non-Aboriginal adults up to 50 years of age.

Analyses for this project are ongoing and a manuscript of these analyses is in early draft stage.

*Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation and the Meningitis Centre*

## VALIDATING AND ENHANCING POPULATION-BASED DATA LINKAGE FOR INFECTIOUS DISEASE RESEARCH

HANNAH MOORE, CHRISTOPHER BLYTH, DEBORAH LEHMANN, PETER JACOBY, FAYE LIM

It is recommended that children admitted

to hospital for a respiratory infection get a laboratory test. In our previous work linking hospital and laboratory data, we found that <60% of records could be linked. The proportions of non-linkage were much higher in some areas than others. Less than 5% of hospital and laboratory records were linked in some remote areas. This project aims to determine whether the high levels of non-linkage were due to children not being tested or due to gaps in the data extraction process.

We have received feedback on the project from members of the Infectious Diseases Community Reference Group and the TICHR Linked Data Users Group. Applications for ethical approval for the project have been submitted.

*Funders of the project: TICHR Small Grant*

## THE KALGOORLIE OTITIS MEDIA RESEARCH PROJECT - AN INVESTIGATION INTO THE CAUSAL PATHWAYS TO OTITIS MEDIA IN ABORIGINAL AND NON-ABORIGINAL CHILDREN

DEBORAH LEHMANN, PETER JACOBY, WENXING SUN, ALICIA ANNAMALAY RUTH MONCK, FIONA STANLEY, IN COLLABORATION WITH BEGA GARNBIRRINGU HEALTH SERVICES, NGUNYTJU TJITJI PIRNI INC, HARVEY COATES, CHRISTINE JEFFRIES-STOKES, ANNETTE STOKES, DANIEL MCAULLAY, DIMITY ELSBURY, JANINE FINUCANE, THOMAS RILEY, SHARON WEEKS, ALLAN CRIPPS, JENNELLE KYD, JACINTA BOWMAN, GERRY HARNETT, DAVID SMITH, GLENYS CHIDLOW, DENISE MURPHY, KYLIE CARVILLE, STEFANO OCCIPINTI, AMANDA LEACH, NEVADA PINGAULT.

Otitis media (OM, middle ear infection) can

seriously affect childhood development, school performance and subsequent social and economic well-being. The Kalgoorlie Otitis Media Research Project was established in 1999 to investigate the causal pathways to OM and, specifically, to identify demographic, socio-economic, environmental, microbiological and immunological risk factors for OM in Aboriginal and non-Aboriginal children in order to develop appropriate interventions. We followed 100 Aboriginal and 180 non-Aboriginal children from birth to age two years. Field work was completed in 2004 and data cleaning completed in April 2005. Analysis of data has been ongoing.

Major findings:

- The peak prevalence of OM in the Kalgoorlie-Boulder area was 72% in Aboriginal children aged 5-9 months and 40% in non-Aboriginal children aged 10-14 months.
- Almost one-third of Aboriginal children and 5% of non-Aboriginal children had a perforated ear drum at least once by age 2 years.
- 65% of Aboriginal children and 23% of non-Aboriginal children have some degree of hearing loss at age 12-17 months.
- Measurement of otoacoustic emissions in early infancy can identify children at subsequent risk of OM.
- Exposure to environmental tobacco smoke is an important risk factor for OM.
- Crowding is the strongest and most consistent predictor of carriage of OM-associated pathogens *S. pneumoniae*, nontypeable *H. influenzae* or *M. catarrhalis*

in the URT, but living in a larger house attenuates this effect in Aboriginal children.

- Daycare attendance predicts carriage of the same OM-associated pathogens in non-Aboriginal children while exclusive breastfeeding for the first 6-8 weeks of life protects children from carriage of *Staphylococcus aureus*.
- Rhinoviruses (HRV) and adenoviruses were commonly identified in asymptomatic children, more commonly in Aboriginal than non-Aboriginal children and are frequently associated with bacterial carriage.
- Human rhinovirus A is the most common virus type identified in healthy children and HRV C is associated with presence of upper respiratory symptoms and carriage of bacteria associated with OM.
- Early carriage of non-typeable *H. influenzae* increases risk of OM in Aboriginal children, while early carriage of *M. catarrhalis* increased risk of OM in non-Aboriginal children.
- A large proportion of *M. catarrhalis* strains were resistant to ampicillin and/or co-trimoxazole. Therefore, current therapeutic guidelines, which recommend amoxicillin for treatment of OM, may need to be revised. We have also documented for the first time simultaneous carriage of multiple strains of *M. catarrhalis*.

*Funders of the project: Western Australian Health Promotion Foundation (Healthway); NHMRC Project Grant #212044 and as part of the NHMRC Program Grant #353514*

## PREVENTING OTITIS MEDIA TO GIVE A SOUND START FOR SCHOOL (PINA PALYA PINA KULILKU, GOOD EARS GOOD LEARNING)

DEBORAH LEHMANN, RUTH MONCK, WENDY SUN, LORRAINE SHOLSON, FAY SAMBO, KIRSTEN ALPERS, TANYANA JACKIEWICZ IN COLLABORATION WITH ANNE MAHONY, CHARLES DOUGLAS, MICHELLE FORREST, DANIEL MCAULLAY, BEGA GARNBIRRINGU HEALTH SERVICES, NGUNYTJU TJITJI PIRNI INC, FRANCIS LANNIGAN, SHARON WEEKS, BRADLEY GILCHRIST, ANNETTE STOKES, CHRISTINE JEFFRIES-STOKES.

This 3-year project follows on from findings of the Kalgoorlie Otitis Media Research Project in which we reported very high rates of otitis media (OM) and associated hearing loss, high carriage of bacteria in the upper respiratory tract (which predisposes to OM) from a very young age in Aboriginal children and an increased risk of OM among children exposed to environmental tobacco smoke. The overall aim is to have Aboriginal children hearing well by the time they start school.

The objectives of this project are to:

1. Develop and implement a multifaceted ear health promotion program in collaboration with Aboriginal organisations in the Goldfields.
2. Evaluate the impact and effectiveness of an ear health promotion program that includes (a) an awareness program, (b) training of health personnel in screening and health promotion and (c) a screening program for OM.
3. Evaluate use at primary health care level of

a simple tool (which measures otoacoustic emissions) that can detect fluid in the middle ear at a very young age and hence identify a target group of children at subsequent risk of developing OM.

4. Evaluate the overall program in terms of feasibility and sustainability.

Over a 3-year period, we conducted 357 ear examinations in Aboriginal children under the age of 5 years. Of the 250 valid examinations, only half had bilateral normal middle ears; 15% had perforated ear drums which is often chronic and can lead to long term hearing loss. A total of 14 soap-making workshops were held in different communities and this activity has been taken up by various organisations and service providers. A series of music workshops, culminating in public performances of a musical, was conducted with school children at 5 locations to promote regular hand washing, keeping cigarette smoke away from children and regular ear screening. Since the launch of the Big Ear (an inflatable ear that children and adults can walk through) in February 2012, it has been used 11 times at community events and schools.

As part of the evaluation of the Pina Palya Pina Kulilku project, we conducted interviews with members of the community at the start of the project and a research assistant who had not been involved in the study interviewed community members towards the end of the study period. At the end of the study period 56% had heard about the project and half of them had attended an activity. Twice as many people reported that ear disease can be prevented by not smoking around children and washing hands than at the start of the

project. The project was well received by the community; they acknowledged that it helped to identify children with hearing problems early and they commented that the development of the musical through workshops was culturally appropriate and effective. Collaboration between different health service providers, education department and wider community has been greatly enhanced through the ear health project.

*Funders of the project: Western Australian Health Promotion Foundation (Healthway)*

## INFECTIOUS DISEASES COMMUNITY REFERENCE GROUP

DEBORAH LEHMANN, HANNAH MOORE, KIRSTEN ALPERS, GLENN PEARSON, ANNE MCKENZIE.

An Infectious Diseases Community Reference Group (CRG) has been meeting at the Institute four times a year since it was convened in 2007. Community members have provided input and advice to researchers who presented on proposed research projects and identified areas of particular community concern e.g. high rates of Chlamydia. As part of informing the wider community about infectious disease research, various presenters including a paediatrician and the Director of TICH, Professor Jonathan Carapetis, addressed the group and discussed current and future issues and directions. The group is comprised of Aboriginal and non-Aboriginal community members, Institute researchers, a representative from the Western Australian Department of Health, a representative from the Vaccine Trials Group (VTG) and a representative from the TICH

Consumer and Community Advisory Council. Outcomes from the work of the CRG in 2012 include a letter of support for a proposed study and the development of plain language summaries of infectious disease research projects at TICHR and VTG.

*Funders of the project: NHMRC Project Grant #572590*

## NEONATAL IMMUNISATION WITH PNEUMOCOCCAL CONJUGATE VACCINE IN PAPUA NEW GUINEA

DEBORAH LEHMANN, PAT HOLT, PETER RICHMOND IN COLLABORATION WITH ANITA VAN DEN BIGGELAAR, WILLIAM SAILA POMAT, PETER SIBA, SUPARAT PHUANUKOONNON, CELESTINE AHO, TILDA ORAMI, JOHN REEDER, AMANDA LEACH, DAVID SMITH, INGRID LAING, GLENYS CHIDLOW.

Throughout the world approximately 800,000 children die annually from pneumococcal disease, the majority in early infancy in third world countries. This study was designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in Papua New Guinean infants at 1-2-3 months of age and to find out whether neonatal immunisation in the first week of life would provide earlier protective antibody responses. We have assessed the impact of neonatal immunisation on humoral and cellular immune responses to concomitant vaccines (diphtheria toxoid, tetanus toxoid and measles) and whether PCV interferes with normal maturation of the immune system. The study is also assessing the impact of a 7-valent PCV (7vPCV) on early pneumococcal nasopharyngeal colonisation. Currently, we are

investigating the impact of neonatal and early infant 7vPCV on pneumococcal serotype-specific mucosal immune responses. A total of 318 children were enrolled; 80% completed follow-up at 18 months of age. Results to date show

- No deleterious effect of neonatal 7-valent PCV (7vPCV).
- 7vPCV is immunogenic in PNG neonates and young infants.
- 7vPCV in a neonatal (0-1-2 months) or early infant (1-2-3 month) schedule primes for immunologic memory for 7vPCV serotypes with booster response to 23-valent pneumococcal polysaccharide vaccine (PPV) at age 9 months. Serotype-specific antibody concentrations are generally sustained to age 18 months.
- PPV induces good antibody responses for some non-PCV pneumococcal serotypes which commonly cause disease.
- 60% of infants were colonised with *Streptococcus pneumoniae* by age 1 month.
- 51 different pneumococcal serotypes have been identified in the upper respiratory tract.
- At age 9 months, 68-78% of pneumococci in the upper respiratory tract were non-7vPCV serotypes.
- PCV has limited impact on upper respiratory tract carriage in this population.
- Early pneumococcal carriage may result in enhanced disease susceptibility and suboptimal vaccine responses by modulating the development of pneumococcal immune responses.

- Analysis of cellular immune responses has shown that neonatal PCV vaccination is safe and not associated with immunological tolerance.

In an extension of this project IA Laing investigated the contribution of human genetic susceptibility to nasal bacterial carriage, development of immune/vaccine responses and the incidence of pneumonia in this population. Preliminary results from investigation of associations between genotype and acute lower respiratory infections (ALRIs) suggest that several genetic variants for known immune pathways may play a role in the frequency of lower respiratory tract infections in children in PNG.

At PathWest Laboratory Medicine WA multiplex PCR has been used to identify viruses in the nasopharynx of trial participants when healthy or during an ALRI episode. Influenza virus A, respiratory syncytial virus and adenoviruses and detection of multiple viruses were more common during episodes of acute lower respiratory tract infections than when children were healthy.

*Funders of the project: This study was funded by the NHMRC/Wellcome Trust International Collaborative Research Grant #303123. Optimisation of mucosal immunity assays in PNG funded by Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant.*

## INVESTIGATION OF SEROTYPE-SPECIFIC ANTIBODY PERSISTENCE AND B-CELL MEMORY AT AGE 3 - 4 YEARS FOLLOWING 23-VALENT

## PNEUMOCOCCAL POLYSACCHARIDE VACCINE AT AGE 9 MONTHS IN PAPUA NEW GUINEAN CHILDREN PREVIOUSLY PRIMED WITH 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

PETER RICHMOND, DEBORAH LEHMANN, PETER JACOBY, ANITA VAN DEN BIGGELAAR, ANGELA FUERY IN COLLABORATION WITH PETER SIBA, WILLIAM SAILA POMAT, ANDREW GREENHILL, CHRISTINE OPA, GERARD SALEU

Recently, concerns have been raised about the role of the 23-valent pneumococcal polysaccharide vaccine (PPV) in infants following priming with a pneumococcal conjugate vaccine due to a potential immunological hypo-responsiveness (i.e. a poorer immune response to subsequent immunisation or natural exposure). In PNG we have previously found that (a) PPV given from age 6 months onwards (without priming with conjugate vaccine) prevents death and severe morbidity due to acute lower respiratory tract infections up to age 5 years and (b) serotype-specific pneumococcal antibody responses are generally sustained up to age 18 months with a PPV booster at age 9 months following priming with 3 doses of 7vPCV. Nevertheless it is important to ensure the immunological safety of the PPV in infants.

This study aims to determine whether PPV given at 9 months of age:

1. provides enhanced persistence of antibody levels associated with protection from invasive disease at 3 to 5 years of age compared to unvaccinated controls
2. has an impact on the development of serotype-specific B-cell memory at 3 to 5

years of age

- enhances antibody persistence and B-cell memory for those serotypes included in 7vPCV among children who received 7vPCV in early infancy
- has an effect on long-term pneumococcal carriage in children primed or not primed with 7vPCV

We are assessing immune function (by measurement of serotype-specific antibody concentrations, opsonophagocytic antibodies and memory B-cell responses) and nasopharyngeal carriage at age 3-5 years prior to and one month after a challenge dose (0.1ml) of PPV in children who took part in the previous neonatal 7vPCV trial (described above) and in 150 age-matched controls. We enrolled 130 of the children who had previously received PPV (primed or not primed with 7vPCV) and 150 controls.

Preliminary data show continuing high pneumococcal carriage up to age 5 years (>70%, predominantly non-PCV serotypes) irrespective of vaccination history, and high serotype-specific pneumococcal antibody concentrations. Preliminary analyses show no evidence of impaired antibody responses following a challenge dose of PPV. These results were presented at the 8th International Symposium on Pneumococci and Pneumococcal Disease held at Iguaçu, Brazil in March 2012.

*Funders of the project: Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant and Merck Sharp & Dohme*

## A STUDY TO DETERMINE THE SAFETY AND IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES IN PAPUA NEW GUINEAN CHILDREN

DEBORAH LEHMANN, ANDREW GREENHILL, PETER RICHMOND, LEA-ANN KIRKHAM IN COLLABORATION WITH PETER SIBA, WILLIAM SAILA POMAT, AUDREY MICHAEL, VELA SOLOMON, WILLIAM LAGANI, TREVOR DUKE, MEGAN PASSEY

Throughout the world approximately 800,000 children die annually from pneumococcal disease, the majority in early infancy. While many industrialized countries have had pneumococcal conjugate vaccines (PCVs) in their routine immunisation schedules since 2001 and a 23-valent pneumococcal polysaccharide vaccine (PPV) has been shown to be efficacious in preventing death and severe disease from age 6 months onwards in Papua New Guinea (PNG), no pneumococcal vaccine is currently offered to children in PNG. The Global Alliance for Vaccines and Immunisation (GAVI) and the World Health Organization (WHO) have committed to the introduction of pneumococcal conjugate vaccine (PCV) for infants in GAVI-eligible countries (including PNG) and introduction of a PCV is planned for 2013-2014.

The primary aim of this study, which began in November 2011, is to determine whether PCV10 and PCV13 (which include 10 or 13 pneumococcal serotypes, respectively) are safe and immunogenic in Papua New Guinean infants for the serotypes in the respective vaccines.

This is an open randomised trial. We aim to enrol 230 children at age 1 month. Half will be

randomised to receive PCV10 and the other half PCV13 in a 1-2-3-month schedule. At age 9 months half in each group are randomised to receive 23vPPV and the other half no PPV. To specifically address the possibility of hyporesponsiveness following PPV, all children will receive a challenge dose (0.1ml) of PPV at age 23 months and followed up 4 weeks later. Pernal swabs to investigate upper respiratory tract carriage and blood for antibody studies and measurement of B- and T-cell responses are collected at ages 1, 4, 9, 10, 23 and 24 months of age. By the end of 2012, 160 children were enrolled in the study and 320 pernasal swabs and 318 blood samples were collected.

*Funder of the project: Exxon-Mobil Governance and Public Affairs.*

## THE AETIOLOGY OF ACUTE LOWER RESPIRATORY TRACT INFECTION AND MENINGITIS IN HOSPITALISED CHILDREN FROM THE EASTERN HIGHLANDS PROVINCE, PAPUA NEW GUINEA

CHRISTOPHER BLYTH, ANDREW GREENHILL, LEA-ANN KIRKHAM, DEBORAH LEHMANN IN COLLABORATION WITH WILLIAM POMAT, TREVOR DUKE, ILOMO HWAHWANJE, HARRY POKA, AUDREY MICHAEL, PAUL HORWOOD, PETER SIBA, PETER RICHMOND, LAURENS MANNING AND JO WAPLING

Pneumonia and meningitis are common and serious diseases of childhood, with significant morbidity and mortality among children under five years of age, particularly in third world settings. *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (Hib) together are estimated to account for two-

thirds of pneumonia and meningitis deaths among children under five. The World Health Organization (WHO) estimates that pneumococcal disease causes approximately 800,000 to one million child deaths annually. Hib is responsible for about 400,000 deaths annually. Hib vaccination was introduced in Papua New Guinea in 2008. An expected decrease in children presenting with proven Hib meningitis has been observed. The Global Alliance for Vaccines and Immunisation (GAVI) and the World Health Organization (WHO) have committed to introduce pneumococcal conjugate vaccine for infants in PNG in 2013-2014.

The primary aim of this study is to determine, using traditional and modern methods, the bacteria and viruses responsible for childhood pneumonia and meningitis in PNG. In addition, we will determine which pneumococcal serotypes colonise the nasopharynx and result in invasive disease. Moreover, we will determine the frequency of antibiotic resistance to guide national empiric antibiotic guidelines. All children undergo a blood culture, blood PCR for pneumococcus and *H. influenzae* and a pernasal swab and children with suspected meningitis have cerebrospinal fluid collected. Following training of the research team in PNG, children with suspected moderate or severe pneumonia presenting to an inpatient or outpatient department and well community controls will be enrolled from January 2013. It is expected that the study will run for at least 2 years and enrol more than 500 children.

*Funder of the project: Pfizer Global.*

## Collaboration for Applied Research and Evaluation

### COLLABORATION FOR APPLIED RESEARCH AND EVALUATION (CARE)

#### OVERVIEW

The Collaboration for Applied Research and Evaluation (CARE) was established by the Telethon Institute in 2000 to progress the translation of research into policy and practice and to conduct high quality policy and practice relevant research based on the priorities of the Health System.

The mission of the Collaboration is to conduct research and provide relevant analysis and interpretation of research information to facilitate evidence based planning, policy and practice to optimise maternal, child and youth health outcomes in Western Australia

The role of the Collaboration is to provide services for health related policy research and development, and program development and evaluation. Those working in the Collaboration have an understanding of issues on both sides of the research to policy and practice continuum. Several of the team have worked in or within government program development and in the service delivery areas, other have extensive experience in specific areas of specialisation in practice and research in areas including maternal health, and Aboriginal and community development and research.

CARE works on research projects and topics of interest to our policy and practice partners and where appropriate, draws on the expertise and experience of TICHR Senior Scientists and external researchers from UWA, Curtin

University and Edith Cowan University. Research ideas and the direction that CARE takes is determined in partnership with our policy and practice partners. These partners include policy and service delivery groups within the Western Australian Department of Health as well as other government and non-government agencies.

### AUSTRALIAN PAEDIATRIC ADHD STUDY: A PILOT

GRANT SMITH AND TANYANA JACKIEWICZ

The primary aim of this pilot study is to assess the methods proposed for the prospective longitudinal study into ADHD diagnosis and treatment in Australia. A successful pilot will allow for funding to be sought for a large-scale prospective study into the diagnosis and treatment of ADHD in Australia. The project will:

The following are elements of the study design:

- Demonstrate the feasibility of using paediatricians to recruit a sample of children with newly-diagnosed ADHD.
- Assess the acceptability of the recruitment processes from the perspective of paediatricians and parents.
- Demonstrate that the recruitment strategy will result in an adequately sized sample and that this sample will include all important sub-populations of the overall clinical population.
- Demonstrate retention of sample. If retention is a problem: identify methods to address attrition (e.g., through interview with parents and paediatricians).
- Identify modifiable barriers to recruitment

and retention.

This project is a pilot project to be conducted in WA; the data from this pilot, along with a separately funded pilot to be conducted in Victoria, will inform the planned Australian prospective cohort study of children with ADHD. The purpose of the pilot is to test the feasibility and acceptability of the study design/ methodology, from the perspectives of both paediatricians and parents

This project is ready to go into the field.

All paediatricians have been recruited. All information materials and tools (online and paper based) have been finalised. Recruitment of parents and children will take place from the end of March until June 2013. The data collection is expected to be completed by June 2013; and the final report is due March 2014.

*Funders of the project: Department of Health*

### RAINE ADHD STUDY 17 YEAR FOLLOW-UP: LONG-TERM OUTCOMES ASSOCIATED WITH THE USE OF STIMULANT MEDICATION IN THE TREATMENT OF ADHD: OUTCOMES AT 17 YEARS OF AGE

GRANT SMITH

This project replicates the methodology used in the report: *Raine ADHD Study: Long-term outcomes associated with stimulant medication in the treatment of ADHD in children*. However, where the previous report examined outcomes measured at the 14-years of age, this project will examine outcomes measured at 17 years of age.

Specifically, this project will aim to use longitudinal data from the Raine Study to

examine the long-term associations between stimulant medication-use during childhood and adolescence and a number of outcomes for children with ADHD. These outcomes, measured at 17 years of age, include: Social, Emotional, Educational, Growth Measures, and Cardiovascular Function. The 17 year follow up also provides an opportunity to examine additional variables such as employment and employment related training, if these additional variables are available.

It is hypothesised that different patterns of medication use will be associated with different outcomes.

All data has been received and analyses have been completed and the final report is currently being prepared. The final report is expected to be completed by April 2013.

*Funders of the project: Department of Health*

### TRIPLE-P PARENTING PROGRAM: LONG-TERM OUTCOMES AND ECONOMIC BENEFITS

GRANT SMITH

This research project will evaluate the Triple-P Program's long term effectiveness, using data collected in the initial effectiveness trial and data on the children and their family up to 13 years following the intervention (children of parents enrolled in the program are now at least 16 years old).

The WA Triple-P study database will be linked to a number of administrative databases (e.g. education, health, mental health, justice, child protection, drug and alcohol, mortality) to determine whether the program was associated

with better long-term outcomes for children.

The project will also use costing algorithms to determine how these outcomes translate into costs/savings to the WA government and develop an overall cost-benefit model of the Triple-P Parenting Program.

The specific hypotheses for this research are:

At the age of 16-17 years, children whose parents received the Triple-P Parenting Program will have:

1. lower number of hospital/emergency department admissions
2. lower levels of teenage pregnancy
3. lower levels of school absenteeism and lower risk of suspension/expulsion from school
4. higher performance on literacy and numeracy tests
5. less contact with the justice system
6. less contact with the mental health system
7. lower incidence of problematic drug/alcohol use

It is hypothesised that improved outcomes associated with the Triple-P program will translate into significant cost savings to the Western Australian government and that the delivery of the program will be associated with a net positive economic impact.

Ethics approval through the Health Research Ethics Committee has been provided. To date, all data has been received from the Department of Health and the WALNA/NAPLAN databases have been received from the Department of

Education. However data from the Department of Corrective Services or the attendance/suspension data from the Department of Education have not yet been received. The custodians of these databases have been contacted to provide a new estimated time of data provision. It is anticipated that receipt of data should occur in February 2013 and no later than March. The project team is still waiting on the costing data from the departments.

*Funders of the project: Department of Health*

## Breathing for Life Study

### RESPIRATORY SYMPTOMS IN CHILDREN AND YOUNG ADULTS WITH CEREBRAL PALSY

IN COLLABORATION WITH DR MARIE BLACKMORE, RESEARCH COORDINATOR, THE CENTRE FOR CEREBRAL PALSY

The aim of this study is to determine the prevalence of respiratory problems in children and adults with CP in Western Australia. This information will be used to identify and intervene as early as possible in order to prevent serious respiratory problems from developing.

The objectives of this study of children and young adults with CP are to determine:

1. the prevalence of respiratory symptoms and morbidity,
2. the risk factors for severe respiratory problems,
3. the prevalence of known risk factors for severe respiratory problems, and
4. the relationships between selected

risk factors, respiratory symptoms and respiratory morbidity.

The study will produce prevalence data on respiratory symptoms, morbidity and risk factors for children, adolescents and young adults with CP by severity of impairment, age and feeding method used. Such data are not currently available in the published literature. The data can be used for early identification and intervention in order to prevent the development of serious respiratory problems. The project will provide a method for tracking changes in these problems over time with a view to identifying early risk factors and protective factors for later serious respiratory problems. Data collection involved completion of a self-report or parental/carer-report questionnaire about respiratory symptoms in young people with cerebral palsy (CP) aged up to 25 years. The data collection phase of the study ended 30 June 2012 as planned. Questionnaires could be completed online or on paper. Approximately 90% were completed on paper. Data from the questionnaires that were completed on paper were entered by members of the research team. Data have been checked and cleaned, and duplicates have been removed. A total of 552 usable questionnaires were received.

Consent to link the questionnaire data to Department of Health data was granted by 87% respondents. The research team expects to receive linked data in January 2013. The final report is currently being prepared and will be completed in June 2013.

*Funders of the project: Department of Health*

## YOUNG ABORIGINAL WOMEN'S

### VOICES ON PREGNANCY CARE (FORMERLY KNOWN AS ESSENTIAL ELEMENTS OF GOOD ANTENATAL CARE: THE VOICES OF YOUNG ABORIGINAL WOMEN)

TRACY REIBEL

This project is being conducted as part of the Aboriginal Maternity Support Services Unit's strategic development to form a comprehensive understanding of what is likely to encourage young pregnant Aboriginal women to access antenatal services. Specific consultation with young (<20 years) pregnant Aboriginal women has not previously been conducted on a wide scale in a range of locations in Western Australia to explore what their views of antenatal care services are.

This project aims to inform the delivery of culturally and age appropriate services that improve access to and sustained use of antenatal services by adolescent Aboriginal women (<20 years).

The main research question is: What are the essential elements of antenatal services that encourage young (<20 years) pregnant Aboriginal women to access antenatal care early in pregnancy as well as continue to access this care.

This project commenced in August 2012, with the first expert reference group meeting held on August 15. An application for approval from the Western Australian Aboriginal Health Ethics Committee (WAAHEC) was submitted to the November and is expected to be approved by January 2013.

Communications have commenced with health

services and organisation across the state to commence community engagement with a view to visiting communities between April and June/ July 2013 to conduct consultations with young women and other parties in a range of locations, including the metropolitan area.

While slow to start, this project has created interest in health services and organisations across the State and it is anticipated that this will assist with both the ethics approval processes, community engagement and recruitment when the time comes to consult with young women in various communities. Community consultations will commence in April 2013 and continue through to July 2013.

*Funders of the project: Department of Health*

## EVALUATION OF THE INTEGRATED SERVICE INITIATIVES TARGETING THE EARLY YEARS IN WESTERN AUSTRALIA

KIM CLARK

There is growing investment in WA in the integration of children's services in recent years with the aim of providing better outcomes for children and families. The emphasis of this growing investment is disadvantaged children and their families, with the goal of achieving greater equity in outcomes for those whose life course may be compromised by environmental factors. However, research suggests that effectiveness of integrated services is highly variable and there is a need to better understand what determines the success of such integrated services and how it relates to children's outcomes. Gathering this evidence will help the State Government to optimise

integration policy by assisting with targeting and with highlighting better practice in the area of program implementation.

This project will explore the provision of children's services in communities, assess how these services work together and evaluate their resulting impact on children's social, emotional and academic functioning across the early years through to early primary (0-8 years). The study will provide insights into how integrated networks can be evaluated and the impact of an integrated approach to service on families' and children's functioning.

The aims of this project are:

1. To obtain a comprehensive measure of service integration within communities based on the Browne et al., (2007) framework by using a variety of measures at various levels of analysis (i.e., structural, functional, outputs).
2. To relate these measures of integration to outcomes at the individual, family, school and community levels.

The study hypothesis is that higher levels of local education, health, and community service integration lead to higher levels of parent and teacher and other service provider role satisfaction and lower levels of developmental vulnerability among children in their first year of full-time schooling living in the lowest SES quintile of school areas in WA.

In accordance with power calculations, approximately 100 public schools will be recruited to participate in this project. Amongst these will be both metropolitan and rural sites. Permission will be sought from the Department

of Education before approaching schools. Service providers, teachers and parents of children (K-3) from participating schools will be asked to complete questionnaires regarding quality of integration and their impacts (see details below). Participation will be voluntary.

The first phase of the project will gather information about the agencies within the community that are involved at the school (e.g., agency sectors, service types, history of service in community, usage history). This will help in quantifying the services used by the school and will be used in determining the scope and depth of integration.

The second phase will involve service providers (e.g., child health nurse, school psychologist, teachers etc.) providing feedback on the scope, depth and quality of the integration. In addition, their perceptions on the impact of integration will be sought. Parents will also answer some questions on how satisfied they are with the services provided and provide information on several outcome measures.

This project has been delayed by ethics approval issues. UWA's ethics committee sought clarification of methodological issues and wanted additional measures taken to ensure parental consent to the release of school records. This required amendments to be resubmitted to subsequent ethics committee meetings, which are only held on a monthly basis. Ethics approval is expected by the end of February 2013. The final report is expected to be completed by April 2014.

*Funders of the project: Department of Health*

## A STUDY EXAMINING POST NATAL FOLLOW UP OF WOMEN RECEIVING PREGNANCY CARE WITH THE WOMEN AND NEWBORN DRUG AND ALCOHOL SERVICE (WANDAS)

ANNA FLETCHER

The aim of this exploratory study is to inform the improvement of the WANDAS service to better facilitate the postnatal access of substance misusing women to health and support services.

The objectives of this study are to:

Determine the pre-disposing individual, organisational and systemic factors that enable or prevent substance misusing women in continuing engagement with WANDAS and other maternal and child health services during the first three months postnatal.

Determine how WANDAS can effectively use already existing resources, relationships or referral pathways to enable increased engagement, beyond the birth period, of substance misusing women and their infants with the range of health and support services they need.

The study uses mixed methods approaches to capture the individual, organisation and system factors that prevent or enable substance misusing women from engaging with WANDAS and other health and support services. These methods include:

[Reviewing client case notes](#) to collect data on clinic attendance, referrals, service engagement and relevant psycho-social information;

[Postnatal brief questionnaire](#) to collect additional postnatal information about the length of time and the level of engagement with



WANDAS as well as any referrals and access to external services (conducted by a WANDAS midwife);

Face to face interviews with 20 WANDAS clients at three months postnatal to explore with participants the barriers and facilitators to their attendance at WANDAS and external health and support services during the postnatal period (conducted by a senior TICHR researcher with a WANDAS midwife present if requested by client); and

Focus groups with Aboriginal health services, primary health services and drug and alcohol support services from the metropolitan area conducted by a senior TICHR researcher. Where possible a mix of health and support workers including, Aboriginal Health Workers, Doctors, Child Health Nurses and drug and alcohol support service workers will be included. The purpose of these will be to investigate current relationships and referral pathways between WANDAS and these services, how referral pathways can be more effective and any strategies that are particularly effective in engaging with vulnerable women and their babies. It is anticipated that four focus groups will be conducted but this is dependent on the numbers recruited.

The sample consists of an estimated 130 women who attend WANDAS for their antenatal care between September 2012 and September 2013. Approximately 35 per cent of the women who attend WANDAS yearly are Aboriginal translating to an estimated 45 women of the overall cohort.

Twenty of the recruited women from the WANDAS client cohort who are deemed by the midwives as coping satisfactorily will be invited

to participate in an in-depth interview.

Four focus groups will be conducted with the consenting health professionals who work with the WANDAS women (General Practitioners, Child Health Nurses, other health and support workers).

The participants will be existing WANDAS clients and will be invited to participate in the research at their first routine antenatal visit by WANDAS midwives if they present at less than 30 weeks gestation. All clients will be fully informed about the research purpose both verbally and with a plain language information sheet that will advise what will be involved. The clients will then be provided with time to consider their participation.

This project began in September 2012. Ethics approval has been provided by Women's and Newborns as well as WAAHEC. The case note review is currently underway. Recruitment is expected to commence in January 2013 and be completed by September 2013. Case file review and interviews with WANDAS clients are expected to be completed by April 2014 with the final report being submitted by November 2014.

*Funders of the project: Department of Health*

### **MATERNAL SATISFACTION WITH PUBLIC MATERNITY SERVICES IN WA (ALSO KNOWN AS WOMEN'S SATISFACTION WITH THEIR MATERNITY CARE)**

KIM CLARK AND TRACY REIBEL

The aims of the project are to develop and pilot a theoretically-framed survey tool for use in monitoring and evaluating women's satisfaction

with maternity services. The proposed outcome is a valid and reliable service evaluation instrument that is capable of aiding the Statewide Obstetric Support Unit in its role of providing quality guidance on maternity models of care across the State.

This project commenced in September 2012 with community consultations with randomly selected women taking place in November 2012 with other planned for January and February 2013. These consultations are expected to be completed by March 2013; with the survey tool development completed by April 2013 and pilot testing of the tool in May 2013. Final report is expected in September 2013.

*Funders of the project: Department of Health*

### **THE DEVELOPMENT OF A NOVEL ANTENATAL EDUCATION PROGRAMME FOR OBESE MOTHERS-TO-BE ON THEIR INTENTION TO MANAGE THEIR GESTATIONAL WEIGHT GAIN AND FOSTER A HEALTHY LIFESTYLE**

ANNA FLETCHER, LISA GIBSON AND TANYANA JACKIEWICZ

The aim of this project is to develop an evidence-based and field-tested antenatal care and education package based on the 'Centering Pregnancy' model that is acceptable to pregnant women with a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>. The package is to be designed with the goal of positively influencing participants' intention to manage and thus minimise their gestational weight gain whilst fostering the adoption of a healthy lifestyle.

The project is consistent with the Department's strategic objectives and would progress the following strategic objectives of the Western Australian Health Promotion Strategic Framework 2007-11 and the National Preventative Health Strategy (2009), that is:

- Ensure women planning pregnancy and pregnant women receive information, education and support to reduce lifestyle risks of excessive weight and poor nutrition.
- Provide consistent and clear information to parents to support them to establish appropriate eating and physical activity patterns in children and to better understand the risks of unhealthy weight in early life through targeted interventions for parents.

The overall project comprises:

- Research and consultation: Formation of a consumer reference group to inform the type of information required and how to present it within a group antenatal education package.
- Development of an antenatal education package: Development of 7 education sessions along with support materials and resources for the target group to cover healthy family lifestyle issues in the antenatal and postnatal periods.
- Preliminary trial of antenatal package content with women to assess acceptance of material covered and method of delivery.
- Evaluation of the intervention with the primary target group through conducting focus groups post each trial session.

The project objectives are:

**Objective 1:** Review of evidence on interventions that have potential application in addressing obesity among pregnant women.

**Objective 2:** Design of a draft antenatal care and lifestyle education package for obese mothers-to-be.

**Objective 3:** Pilot-testing of each session in the maternal obesity education package with members of the target group recruited from KEMH.

The anticipated project outcome will be an evidence-based specifically designed education package (7 sessions) that can be piloted that encourages women to change their behaviour for healthy pregnancy weight gain.

All seven sessions have been developed and trialled and re-trialled with eligible women. The sessions were informed by the outcomes of the consumer reference group consultation, the preliminary trials of each session, the steering committee input and the motivational interviewing training attended by the project managers. Changes to the programme's written package were also made.

Due to the initial recruitment process taking longer than anticipated the project team applied for an amendment to the recruitment protocol. This allowed for eligible women to be cold-called by the research midwife and to provide a verbal response as to whether they are interested in hearing more about the study rather than posting in a decline slip. This amended protocol saved 2 weeks from each recruitment drive.

Along with the 6 antenatal sessions, a 7<sup>th</sup> session was developed for the postnatal follow-up. It

was identified that a postnatal session would be of value for the target group to reinforce healthy behaviour changes they made during pregnancy and extend into the postnatal period. A trial and re-trial of the postnatal session has also taken place.

The finalisation of the drafted participants' guide and facilitators' handbook for each session is to be completed following receiving feedback from the steering group, relevant health professional and consumer reference group, where appropriate. The final report is anticipated to be completed in May 2013 as well as publication of two papers.

*Funders of the project: Department of Health*

## THE PSYCHOSOCIAL DETERMINANTS OF HEALTH OUTCOMES IN YOUNG CHILDREN WITH CYSTIC FIBROSIS (CF)

IN COLLABORATION WITH DR TONIA DOUGLAS AND CATHERINE GANGELL FROM CYSTIC FIBROSIS RESEARCH GROUP AT PMH, CARE LEADS: GRANT SMITH

The primary aim of this pilot study is to gather data to inform the design and implementation of a longitudinal research project examining the relationships between psychosocial factors and the progression of CF lung disease.

To meet this aim, a primary cross sectional study of preschool children diagnosed with CF through NBS and their families in Western Australia will be conducted to gain insight into the relationships between psychosocial factors and disease progression. Information will be gained through one-to-one interviews of parents of

children with CF and through self-administered questionnaires.

The specific objectives for the project are:

- To identify the cross-sectional relationships between child health measures (designed to measure the progression of CF), and the following psychosocial measures: family functioning, parental mental health, parental reflective functioning, and dyadic relationships.
- To use novel and sensitive techniques to detect and quantify disease progression/severity in young children with CF.
- To determine the value and precision of each of the psychosocial instruments as correlates of health status in early life and inform the choice of instruments for the longitudinal study.

Ethics documentation has been prepared and tools have been designed. HREC has provided ethics approval to recruit and collect data.

Findings of this primary cross-sectional study will be presented to the CF clinic at Princess Margaret Hospital and interpreted within the context and limitations of the study design. We anticipate that results will inform the CF multidisciplinary team of significant links between disease progression and specific psychosocial domains within this population of children. We anticipate that this information will provide the foundations for design of psychosocial screening tools and intervention strategies on a local level, which will be further developed with the results of the longitudinal study. Data collection is underway with 50% of participants having completed and returned

their questionnaires.

*Funders of the project: Department of Health*

## Newly Approved Projects (end of 2012)

These projects have recently been approved by the Western Australian Department of Health and will form the program of work for CARE for 2013 and 2014. The research has yet to commence.

### CHOICE IN MATERNITY MODELS OF CARE:

#### A PRAGMATIC RANDOMISED TRIAL OF STANDARD CARE VS MIDWIFERY GROUP PRACTICE AT KALEEYA HOSPITAL AND FIONA STANLEY HOSPITAL

TANYANA JACKIEWICZ AND TRACY REIBEL

This study aims to:

1. Determine the effect of choice of maternity (standard care or Midwifery group practice (MGP)) model of care on the satisfaction (experience, expectations (whether met or unmet), and perceptions) of women attending maternity services at Kaleeya Hospital (and Fiona Stanley).
2. Determine whether there are any characteristics of the woman or the care that she receives that are predictive of a positive maternity experience (for both MGP and standard care).
3. Describe the Midwifery group practice program as it has been implemented at

Kaleeya Hospital and document the views, opinions and attitudes of midwives who work within the MGP over the trial period.

Satisfaction is a complex concept and consists of a number of constructs. This study will employ a tool that is currently being developed by TICHR which involves determining satisfaction through measuring a number of experiential, perceptions and expectancy fulfilment constructs.

This Study takes a close look at the effect of CHOICE on self-rated "satisfaction" (construct that includes experience, expectations (whether met or unmet) and perceptions) of maternity care provided at Kaleeya Hospital (and Fiona Stanley).

It will describe personal and other characteristics of a woman that predicts whether that woman will have a positive maternity experience as well as describe the characteristics of the model of care that predicts whether a woman will have a positive maternity experience.

This Study will also determine whether the MGP has been implemented as intended and whether midwives report greater personal and professional satisfaction with the MGP compared with standard care (Process Evaluation).

The study design incorporates three components:

1. A two armed comparative study of satisfaction of women who are provided with a choice in their maternity care (MGP vs standard care); compared with those who are not provided with a choice (MGP vs standard care).
2. A comparative study of the satisfaction

of women who are enrolled in the MGP compared with those who are enrolled in standard care (independent to choice).

3. A process evaluation of the MGP model to determine how well the model has been implemented at Kaleeya according to the original design including the experiences of midwives working within the model.

The trial will produce the following outcomes:

1. Information on woman's experiences (positive and negative), expectations and acceptability with the different models of care offered at Kaleeya (and Fiona Stanley) that

[a] provide evidence to SMHS to continue to support the provision of choice (including MGP) for women who birth within the catchment area and

[b] inform improvements in all the models of care offered at Kaleeya (and Fiona Stanley) to better meet individual women's needs.

2. Information on the characteristics of the model of care under the different experimental conditions (choice and no choice; MGP and standard care) that predicts whether a woman reports a positive maternity experience?
3. Information on the factors associated with the actual antenatal and birthing (as verified by administrative records) experience that affect a woman's satisfaction with her model of care.
4. What personal variables predict whether women will find their expectations met or unmet under the different experimental

conditions (choice and no choice MGP and under standard care (i.e. are the models better suited to different groups of women)?

*Funders of the project: Department of Health*

## EVALUATION OF THE CHOICE AND PARTNERSHIP APPROACH (CAPA) WITHIN THE ROCKINGHAM AND SWANS CHILD AND ADOLESCENT MENTAL HEALTH SERVICES

GRANT SMITH AND TANYANA JACKIEWICZ

The aim of this project is to conduct a comprehensive evaluation of CAPA across the two trial sites in the Perth Metropolitan Area. The evaluation aims to document the effect of CAPA on:

1. clients and their families, CAMHS service,
2. CAMHS staff,
3. external referrers (to CAMHS), and
4. external referral services (from CAMHS).

The evaluation will consist of both process and outcome/impact components.

The Process Evaluation research questions are as follows:

- What preparatory work/resources were required prior to CAPA implementation?
- How were decisions made around tailoring flexible elements of the program to suit local need?
- What change management strategies were employed and how effective were these?
- What were the barriers and facilitators

to implementing various components of CAPA?

- How well have the elements of CAPA been implemented?
- How did the implementation of CAPA differ across the two sites?

The Outcome/Impact research questions are as follows:

How did the introduction of CAPA affect the following?

### Children and families referred to CAMHS

- Clinical pathway
- Timeliness of first clinical appointment
- Dose of clinical contact
- Success in access to referral services
- Perceived effectiveness of treatment

### CAMHS Service

- Waiting list
- Number of referrals
- Number of cases engaging with CAMHS services
- Number of re-referrals
- Caseload management characteristics
- Non-clinical time

### Referrers to CAMHS

- Opinions on CAMHS intake criteria
- Satisfaction with referral outcomes

- Perceptions of CAMHS responsiveness

#### Referral services (from CAMHS)

- Number of referrals
- Waiting list
- Appropriateness of CAMHS-referred clients
- Perceptions of CAMHS responsiveness

The evaluation is expected to produce the following outcomes:

Information on:

1. the influence of CAPA clinical pathways for CAMHS clients,
2. the impact of CAPA on a number of clinical outcomes for clients of CAMHS, and;
3. perceptions of the impact of CAPA on services downstream from CAMHS. This information will be invaluable for CAMHS services deciding on management strategies for managing demand and capacity.

The results of the process evaluation will provide valuable information that other CAMHS sites across WA and Australia, and internationally, can use to inform the successful implementation of CAPA whilst reducing disruption to the service. It may also indicate those aspects of the model that are 'successful' and those that are problematic; potentially allowing the development of a more refined model of service delivery for WA CAMHS.

*Funders of the project: Department of Health*

## ANAEMIA IN WESTERN AUSTRALIA: INCIDENCE IN ABORIGINAL AND NON-ABORIGINAL POPULATIONS ACROSS THE STATE

GRANT SMITH

The major aim of this study is to use existing full blood count data to identify diagnoses of moderate to severe anaemia in children across Western Australia. Differences across subpopulations of the state will be examined to identify risk factors for anaemia and identify significant differences across Western Australian communities (particularly remote/rural Aboriginal communities). Where possible, incidence rates of various *subtypes* of anaemia will be also be examined.

Meeting the above aim is reliant on the practices of health service providers in Western Australia. As such, the study aims, in the first instance, to document policies and practices employed in the diagnosis and treatment of anaemia across Western Australia and compare these to best practice.

The project will seek to address the following research questions:

- What practices are employed in the screening and diagnosis of anaemia in Western Australia?
  - How do these differ by health service providers?

How do these differ over regions/communities?

- What is the overall incidence rate of moderate to severe anaemia across Western Australia?

- Has the rate of moderate to severe anaemia in WA changed over the past 5 years?
- Are the following characteristics predictive of a higher incidence of moderate to severe anaemia:
  - Rural/remote primary place of residence?
  - Great levels of disadvantage in primary place of residence?
  - Aboriginal status?
- Are there *specific* rural/remote, predominantly Aboriginal communities with disproportionately higher incidence of moderate to severe anaemia in Western Australia?
- What proportion of moderate to severe anaemia diagnoses are:
  - Macrocytic, microcytic, normocytic;
  - Present with an abnormal white cell count;
  - Accompanied with hospitalisation for a 'bleeding'-related diagnosis

The outcomes of the research include:

1. An indication of the practices/protocols in place around the diagnosis of anaemia in Western Australia;
2. The first reliable state-wide indication of the incidence of diagnosed moderate to severe anaemia in Western Australia;
3. Estimates of incidence of diagnosed moderate to severe anaemia in specific WA communities;

4. Identification of risk factors for diagnosed moderate to severe anaemia in Western Australia;
5. Identify the average age of diagnosis and how this differs across groups;
6. A broad description of the proportion of moderate to severe anaemia subtypes across populations in WA;
7. An estimation of the *likely* rates of mild anaemia across WA.

*Funders of the project: Department of Health*

## STRONG SPIRIT STRONG FUTURES EVALUATION

TANYANA JACKIEWICZ, TRACY REIBEL AND KIM CLARK

*Strong Spirit Strong Future (SSSF)* is the state-wide Aboriginal fetal alcohol spectrum disorder (FASD) Prevention Program, coordinated by the Drug and Alcohol Office (DAO). Funding of \$2.23 million over a four year period (2009/10 to 2013/14) has been allocated to develop a suite of Aboriginal FASD prevention initiatives. The project funding was made available through the Council of Australian Governments (COAG) Indigenous Early Childhood Development National Partnership Agreement. No funding was provided to evaluate any component of the program through the COAG funding.

The social marketing component is aimed at raising community awareness of the National Health and Medical Research Council (NHMRC) 2009 guidelines stating that the safest choice is not to drink alcohol when pregnant, planning a pregnancy or breastfeeding. This campaign was

first aired on TV and radio in September 2011 and will be repeated in September 2012.

The aim of this evaluation is to determine whether the stated aims and objectives of the Strong Spirit Strong Future Prevention Program have been met according to the internal and external stakeholders relevant to the Program. This research will inform the development of a best practice resource (or guidelines) based on the experiences of the SSSF Program that can be used to plan future health promotion campaigns targeted at Aboriginal people.

*Funders of the project: Department of Health*

## Developmental Pathways in WA Children Project

FIONA STANLEY (UNIVERSITY OF WESTERN AUSTRALIA (UWA), TELETHON INSTITUTE FOR CHILD HEALTH RESEARCH (TICHR)); HELEN LEONARD (UWA, TICHR); NICHOLAS DE KLERK (UWA, TICHR); JIANGHONG LI (CURTIN UNIVERSITY OF TECHNOLOGY, TICHR); NATASHA NASSAR (UWA, UNIVERSITY OF SYDNEY); STEPHEN ZUBRICK (UWA, TICHR); CATHERINE TAYLOR (UWA, TICHR); AMANDA LANGRIDGE (UWA, TICHR); EDDIE BARTNIK (WA MENTAL HEALTH COMMISSION); CHERYL GWILLIAM (WA DEPARTMENT OF THE ATTORNEY GENERAL); IAN JOHNSON (WA DEPARTMENT OF CORRECTIVE SERVICES); TIM MARNEY (WA DEPARTMENT OF TREASURY AND FINANCE); KARL O'CALLAGHAN (WA POLICE); SHARYN O'NEILL (WA DEPARTMENT OF EDUCATION); GRAHAME SEARLE (WA DEPARTMENT OF HOUSING); RONALD CHALMERS (DISABILITY SERVICES COMMISSION WA); JENNI PERKINS (WA DEPARTMENT FOR COMMUNITIES); CLIFF WEEKS (WA DEPARTMENT OF INDIGENOUS

AFFAIRS); DIANA ROSMAN (DEPARTMENT OF HEALTH WA); AND KIM SNOWBALL (DEPARTMENT OF HEALTH WA)

The Developmental Pathways Project is a landmark project taking a multidisciplinary and holistic approach to investigate the pathways to health and wellbeing, education, disability, child abuse and neglect, and juvenile delinquency outcomes among Western Australian children and youth. To achieve this, researchers from the Telethon Institute for Child Health Research and the University of Western Australia have been working in collaboration with a number of state government departments, including the WA Departments of Health, Education, Child Protection, Corrective Services, Communities, Indigenous Affairs, Treasury and Finance, Housing, Attorney General, the Disability Services Commission, the Mental Health Commission, and WA Police. The project has established the process of linking together de-identified longitudinal, population-based data collected and stored by a large number of these WA government departments and the Telethon Institute, to create a fantastic cost-effective research and policy planning/evaluation resource. The project has also established a Directors' General Steering Committee who meet twice a year to discuss how to best use these joined up data and joined up agency resource. The project also has a Consumer and Community Reference Group who meet four times a year to provide an oversight role for governance, standards and practices relating to the project from a community perspective.

The linked data are being used by researchers and the respective departments to identify multi-level and early determinants

of developmental outcomes and the interrelationships among them. Through the effective communication of the research findings, future government agency policies, practice and planning initiatives will be more preventative, culturally appropriate and cost efficient, and we have encouraged cross-agency collaboration to ensure improved health, wellbeing and development of children and youth, their families and their communities.

*Funders of the project: The Developmental Pathways Project was made possible by the generous cash and in-kind contributions made by all of the collaborating organisations and government departments, which has been matched by the Australian Research Council (ARC) through two consecutive ARC Linkage Project Grants.*

The Developmental Pathways Project supports several postgraduate students and postdoctoral fellows, to conduct individual research projects which answer specific research and policy relevant questions within and across the themes and scope of the overall project.

## CHILD ABUSE AND NEGLECT

DR MELISSA O'DONNELL

Dr Melissa O'Donnell is an NHMRC Early Career Fellow and a Psychologist who completed her PhD in 2009 through the University of Western Australia. Her research uses longitudinal population data provided through the Developmental Pathways Project. This administrative data is being used to: investigate emergency department presentations and hospital admissions related to child abuse and neglect; determine the mental health and

juvenile justice outcomes of children who have contact with the child protection system; and investigate the child, family and community characteristics which increase or reduce vulnerability to child abuse and neglect.

MIRIAM MCLEAN

Miriam McLean is completing her doctorate on the Developmental Pathways Project. Her project is titled "Educational outcomes of children in contact with the child protection system: A longitudinal population study". The aim of this study is to examine the educational outcomes of children in contact with the child protection system. This project is innovative in that it will use linked government administrative data from Child Protection, Health, Education and Disability Services through TICHR's Developmental Pathways Project, to conduct a longitudinal analysis of prospective data from a large cohort of children. Currently, Western Australia is the only Australian state that has a comprehensive data linkage system including children's education and child protection data, along with data on an array of child, parental and community characteristics. Using this linked data will assist in overcoming the many methodological difficulties associated with maltreatment research, and enable a much greater understanding of the relationships between maltreatment and out of home care with educational outcomes, taking into account a range of risk factors at the child, parental and community levels.

## ABORIGINAL HEALTH RESEARCH

GLENN PEARSON

Glenn Pearson, a Noongar from Western Australia, and Manager of Aboriginal Health Research at the Institute, is completing his Doctorate on the Developmental Pathways Project. His qualitative research PhD project explores how the delivery of health, education and child protection services provided by the WA State Government to Aboriginal clients is mediated by the perceptions Non Aboriginal and Aboriginal people hold of themselves and each other in the provision and receipt of these services.

#### JOCELYN JONES

Jocelyn Jones is completing her doctorate through the Developmental Pathways Project. Her project is titled 'Exploring the pathways to contact with juvenile justice in Aboriginal and Torres Strait Islander children: developing a profile of the risk and protective factors to support a strategy for change'. Using linked longitudinal population data provided through the DPP this project seeks to develop a profile of the developmental, health, socio-economic, racial and demographic factors associated with risk, protective and resilience factors that contribute to juvenile delinquency in Aboriginal and Torres Strait Islander Children.

#### JUVENILE DELINQUENCY

##### ANNA FERRANTE

Anna Ferrante is an Associate Professor at the Centre for Data Linkage, Curtin University, formerly a Research Associate Professor at the Crime Research Centre, University of Western Australia. As part of the Developmental Pathways Project, Anna is undertaking a

population-based study of the dimensions and development of delinquency in Western Australian children. The aim of the project is to contribute to a better understanding of the dimensions of juvenile delinquency and of the impact of various factors on the development of delinquency over the life-course. By exploring the interactions between risk factors and their effect on offending, it may be possible to map 'pathways' from early childhood to juvenile delinquency and later criminal behaviour.

#### ATTENTION DEFICIT HYPERACTIVITY DISORDER

##### DR DESIREE SILVA

Dr Desiree Silva is a paediatrician, and Professor of Paediatric Medicine at Joondalup Health Campus and UWA. Due to the escalation of mental health issues in children, Desiree commenced a PhD through UWA and the Telethon Institute for Child Health Research on the risk factors and outcomes of children and adolescents diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) in Western Australia. Her PhD project uses longitudinal population data provided through the Developmental Pathways Project. This administrative data, along with questionnaire data, is being used to: identify potential antenatal and early neonatal risk factors associated with children requiring treatment with stimulant medication; explore hospital and emergency morbidity, accident related hospitalisation risk, criminal and antisocial behaviour, and service needs associated with children on stimulant treatment for ADHD; examine education outcomes of children diagnosed with ADHD and their level of

stimulant medication treatment; and explore the mental health burden of parents and family functioning of children diagnosed and treated with pharmacotherapy for ADHD in WA.

#### MENTAL HEALTH

##### JANICE WONG

Janice Wong is completing her doctorate on the Developmental Pathways Project. Her project is titled 'The relationship between educational and mental health outcomes for Western Australian children: A longitudinal population study'. Using linked longitudinal population data provided through the DPP, this subproject seeks to explore the dynamic relationship between children's educational outcomes and their mental health, whilst taking into account variables that have been shown to impact on this relationship. Children who are vulnerable to mental health problems are subsequently at risk of experiencing interference with development, and more specifically, with schooling, and the development of their identity. Results of this study will potentially inform the development of suitable interventions, ultimately with the aim to decrease the prevalence of mental health issues and improve educational outcomes.

##### NAN HU

Nan Hu is completing his doctorate on the Developmental Pathways Project. His project is titled "An investigation of the developmental pathways to hospitalized deliberate self-harm behaviours (DSH) among young people: a birth cohort study using cross jurisdictional linked data in Western Australia (WA)". This

project has two main aims: 1) To examine the epidemiological characteristics and the current trend of deliberate self-harm related hospitalizations in young people of 10-30 years old in Western Australia. 2) To investigate how specific biological, psychological and social factors at the child, family, school and community levels interact to influence the developmental pathways to deliberate self-harm related hospitalization among young people. This aim will be achieved by undertaking five sub-studies respectively focusing on birth factors, family and community factors, child maltreatment, educational outcome, psychiatric correlates, and certain types of intellectual and developmental disabilities.

The Developmental Pathways Project also facilitates the provision of de-identified non-health linked population level data to a number of other research projects conducted within other research institutions and WA Government, including those led by Prof Jablensky (Pathways of Risk from Conception to Disease: A Population-Based Study of the Offspring of Women with Bipolar Disorder and Schizophrenia); Assoc Prof Tony Butler (Does Traumatic Brain Injury (TBI) lead to offending behaviour?); and Dr Colleen O'Leary (Investigating the effect of a maternal alcohol-related diagnosis on the educational, juvenile justice, and child protection outcomes of their children and Examining the effect of the dose, pattern, and timing of prenatal alcohol exposure on educational outcomes). We are assisting the WA Mental Health Commission in an evaluation of Supported Accommodation Services for people with severe and persistent mental health problems, to try to ascertain if supported

accommodation results in improved health and mental health for residents. We are also working with Ngala to investigate where their services are being most utilised.

In 2012 we were involved in the WA Crime Prevention initiative and provided information and presentations to the WA Crime Prevention Council on hotspots for Juvenile crime, and areas in the WA metropolitan area which are in need of extra support and services for families and children.

## Human Capability

### GETTING OUR STORY RIGHT

DAVID LAWRENCE, FRANCIS MITROU, DANIEL CHRISTENSEN, GLENN PEARSON

The Getting Our Story Right project is a collaboration between the Telethon Institute for Child Health Research, the Australian Bureau of Statistics (ABS) and The Department of Health WA (DoHWA) and aims to explore and develop different methods for deriving Indigenous status from multiple data sources using the WA Data Linkage System and examine the impact of these methods on a sample of health and educational outcomes among the Indigenous population.

Various methods of deriving consistent Indigenous status from a linked data source will be explored and the impact of these methods examined against a selection of health and educational outcomes such as mortality rates, hospitalisation rates, and school-based reading and writing scores from standardised tests.

The overall aim of the project is to produce a set of recommendations for agencies and

researchers responsible for the provision of Aboriginal and Torres Strait Islander Statistics, particularly with reference to COAG 'Closing the Gap' indicators. It is envisaged that these recommendations will help agencies and researchers produce consistent, reproducible and meaningful statistics in order to assess the health and wellbeing of Aboriginal people.

*Funders of the project: COAG, ARC Discovery Grant DP0877513*

### SUGAR SWEETENED BEVERAGE CONSUMPTION BY AUSTRALIAN CHILDREN: IMPLICATIONS FOR PUBLIC HEALTH STRATEGY

KATHERINE HAFEKOST, FRANCIS MITROU, DAVID LAWRENCE AND STEPHEN R ZUBRICK

Consumption of sugar sweetened beverages (SSB) has been linked to unhealthy weight gain and nutrition related chronic disease. Despite public health efforts to reduce consumption, such as limiting sales of these products in schools and restrictions on marketing, Australian children's intake remains high. In addition, little up-to-date information about the primary purchase source of SSB, consumption patterns and the dietary and demographic profile of SSB consumption in children was available. We used data from the 2007 Australian National Children's Nutrition and Physical Activity to address these issues.

We found that SSB consumption was high and patterns of consumption varied by age. The primary source of SSB was from supermarkets with less than 17 per cent of products being sourced from fast-food establishments and school canteens. Further, the majority of SSBs

were consumed at home. We found children whose parents had lower levels of education consumed more SSB on average, while children whose parents had higher education levels were more likely to favour sweetened juices and flavoured milks.

This research highlights the need for public health interventions which are evidence based and target the primary source of SSBs in order to reduce current levels of intake by Australian children. Additionally, education of parents and children regarding the health consequences of high consumption of both carbonated and non-carbonated SSBs is required.

*Funders of the project: NHMRC program grant #572742*

### PLAYGROUP PARTICIPATION AND THE ASSOCIATED OUTCOMES FOR CHILDREN AND MOTHERS

KIRSTEN HANCOCK, DAVID LAWRENCE, FRANCIS MITROU, STEPHEN R. ZUBRICK, WITH DAVID ZARB, JAN NICHOLSON AND DONNA BERTHELSEN

Though thousands of parents and children attend playgroups each week, there is little evidence around the extent to which playgroups achieve their objectives of enhancing child development, supporting parents and encouraging community participation. Using data from the *Growing Up in Australia: The Longitudinal Study of Australian Children*, we found that children from disadvantaged families were less likely to access playgroups than other children, yet these were the children who benefitted most from attending. Our results also suggest that socially isolated parents may

find playgroups a useful resource to build their social networks, and that children attending playgroups tended to have more books in the home, attended more activities outside the home, lived in safer neighbourhoods and in places with good access to basic services, and to use other child services (like a maternal child health nurse).

*Funders of the project: NHMRC program grant #572742*

### HOW MULTIPLE GENERATIONS OF MENTAL HEALTH PROBLEMS IN FAMILIES INFLUENCES THE WELLBEING OF CHILDREN

KIRSTEN HANCOCK, FRANCIS MITROU, DAVID LAWRENCE AND STEPHEN R. ZUBRICK, WITH MEGAN SHIPLEY

Research has consistently shown that children of parents with mental health problems are at greater risk of also developing mental health problems. Yet there is limited research around how these mental health relationships evolve over multiple generations, beyond the initial parent-child relationship. In this study, we used data collected from 4,600 families participating in *Growing Up in Australia: The Longitudinal Study of Australian Children* to examine the mental health relationships across three generations of Australian families. Our results show that the mental health of grandparents matters for children, even in the absence of problems in the parent generation. In our next phase of work we are examining how multiple generations of mental health problems impact upon specific mental health problems for children, such as conduct problems or emotional

problems, and how these differ according to mental health on the maternal and paternal side of families.

*Funders of the project: NHMRC program grant #572742*

## THE INFLUENCE OF LONG-TERM JOBLESSNESS AND SEPARATION OF GRANDPARENTS ON GRANDCHILDREN

KIRSTEN HANCOCK AND STEPHEN R. ZUBRICK, WITH BEN EDWARDS (AUSTRALIAN INSTITUTE OF FAMILY STUDIES)

We have understood for many years that family experiences such as separation and/or joblessness have close intergenerational links. To date, there have been limited opportunities to examine how these intergenerational relationships work across three generations of family members. In collaboration with the Australian Institute of Family Studies, this project uses data from over 8,000 families participating in *Growing Up in Australia* and examines the extent to which joblessness and family separation transfers across generations, and how a continuing family history of these disadvantages relates to a variety of outcomes for children, including their social and emotional wellbeing and performance at school. The initial findings from the project will be published in the Longitudinal Study of Australian Children 2012 Annual Statistical Report.

*Funders of the project: NHMRC program grant #572742*

## STUDENT ATTENDANCE AND

## EDUCATIONAL OUTCOMES OF WESTERN AUSTRALIAN STUDENTS

KIRSTEN HANCOCK, CARRINGTON SHEPHERD, DAVID LAWRENCE AND STEPHEN R. ZUBRICK, WITH THE WESTERN AUSTRALIAN DEPARTMENT OF EDUCATION

Regular attendance at school provides children with the basic skills for learning, and assists the development of social skills including communication, self-esteem, teamwork and friendship building. As attendance is a precursor for onward skill development, it is important to understand how patterns of attendance are established in the early years and the nature of the relationship between attendance and achievement, so that learning opportunities for all students can be maximised. We used WA Department of Education enrolment, attendance and NAPLAN achievement data from 2008 to 2012 to assess the attendance patterns of over 415,000 primary and secondary students across the 5-year period, and how these patterns vary for students with different characteristics. We examine the extent to which authorised and unauthorised absences from school are related to NAPLAN achievement after controlling for a range of factors. We investigate how absence rates in previous years relate to current achievement levels, whether there is a “safe” threshold of absence for students, and whether students who improve their attendance at school improve their NAPLAN scores. The results of the study have important implications for students, parents and educators, and will be available mid-2013.

*Funders of the project: Australian Government Department of Education, Employment and Workplace Relations.*

## HIGHLY PROTECTIVE PARENTING AND CHILD BMI

KIRSTEN HANCOCK AND STEPHEN R. ZUBRICK

In recent decades rates of child overweight and obesity have increased, while children have become less active and more sedentary. Over the same period, parents have become increasingly concerned for children’s safety and independent mobility, even though the risks of harmful events have not changed. Though some have argued that a trend towards overprotective parenting, and subsequent restrictions on children’s independent mobility, may be linked to the increase in rates of child overweight and obesity, there is very limited research available to support these claims. The aim of this study is to establish if any association can be drawn between child obesity and maternal protectiveness. Our initial findings suggest that maternal overprotection is more common amongst disadvantaged families, and that as children become older, the body mass index of children with highly protective mothers increases at a faster rate compared to other children. The results provide evidence of a link between maternal protectiveness and child BMI, however further research is required to understand the mechanisms that underpin this link.

*Funders of the project: NHMRC program grant #572742*

## MEASURING AND MODELLING THE CHILDHOOD DETERMINANTS OF HUMAN CAPITAL FORMATION AND HUMAN CAPABILITY EXPANSION

STEPHEN R. ZUBRICK, SVEN SILBURN, DENNIS TREWIN, ANN SANSON, BILL LOUDEN, DAVID LAWRENCE

This study uses archival data sources and data linkage capacities to focus on the measurement of human capability across the life course. Specifically the study aimed to integrate archival data with population data registers in the health, education and social services sectors to study patterns of participation associated with specific education, health and developmental burdens; and to use national data sources such as the Longitudinal Study of Australian Children to compare and validate findings across settings. This study seeks to document the relationship of human capital growth to educational attainment, employment and occupational skill level across the lifespan and how this relates to human capability expansion. The study also sought to inform population health interventions and health promotion through a lifecourse approach to informing the evidence base for these interventions.

*Funders of the project: COAG, ARC Discovery Grant DP0877513*

## CHILD AND ADOLESCENT COMPONENT OF THE NATIONAL SURVEY OF MENTAL HEALTH AND WELLBEING

KATRINA BOTERHOVEN DE HAAN, SARAH JOHNSON, JENNIFER HAFEKOST, DAVID LAWRENCE, STEPHEN R. ZUBRICK

The National Survey of Mental Health and Wellbeing includes three main components - a population-based survey of adults, a service-based survey of people with low-prevalence



psychotic disorders, and a population survey of children. The first Child and Adolescent component was conducted in 1998. The Institute won a tender process to conduct *Young Minds Matter*, the second child and adolescent component of the National Survey of Mental Health and Wellbeing. Content development, sample design and pilot testing have been completed and the survey is scheduled to go into the field mid-2013.

The broad aims of the National Survey of Mental Health and Wellbeing initiative have been to determine how many Australians have which mental disorders, what is the impact of these disorders (on individuals, families and communities), and what services are being used by people with mental disorders.

*Funders of the project: Australian Government Department of Health and Ageing*

## EARLY LIFE INFLUENCES ON CHILD AND ADOLESCENT MENTAL HEALTH PROBLEMS: A LIFE-COURSE APPROACH TO PREVENTION AND INTERVENTION

DR MONIQUE ROBINSON (SUPERVISOR: W/ PROFESSOR STEPHEN R. ZUBRICK)

It has been suggested that the best method for avoiding poor mental health outcomes is to build and promote positive outcomes right from the very start of life. The goal then shifts from treating problems after they have occurred, to a model enabling the formation and promotion of positive mental health outcomes. However, we have predominantly used early childhood as the start point for development. This project exists within this new paradigm, exploring the early life

influences on behavioural development.

*Funders of the project: Australian Rotary Health Colin Dodds Postdoctoral Research Fellowship (2011-2013) and NHMRC Early Career Fellowship (2013-2016)*

## PARENT-CHILD BOOK READING ACROSS EARLY CHILDHOOD AND CHILD VOCABULARY IN THE EARLY SCHOOL YEARS: FINDINGS FROM THE LONGITUDINAL STUDY OF AUSTRALIAN CHILDREN

BRAD FARRANT, STEPHEN R. ZUBRICK

Vocabulary knowledge is a critical component of school readiness. The current study investigated the extent to which low levels of joint attention in infancy and parent-child book reading across early childhood increased the risk of children having poor vocabulary around the time of school entry (using data from the Longitudinal Study of Australian Children). As hypothesised, children who had low levels of joint attention at wave 1 were significantly more likely to have poor receptive vocabulary at wave 3. Furthermore, children who had low levels of parent-child book reading across early childhood were two and a half times more likely to have poor vocabulary at wave 3. These results converge with the findings of training studies and underline the importance of educating current and future parents about the pivotal roles of joint attention and parent-child book reading for children's language development and hence their readiness for school.

*Funders of the project: NHMRC Program Grant #572742*

## LANGUAGE, COGNITIVE FLEXIBILITY, AND EXPLICIT FALSE BELIEF UNDERSTANDING: LONGITUDINAL ANALYSIS IN TYPICAL DEVELOPMENT AND SPECIFIC LANGUAGE IMPAIRMENT

BRAD FARRANT, MURRAY MAYBERY, JANET FLETCHER

The hypothesis that language plays a role in theory of mind (ToM) development is supported by a number of lines of evidence. The current study sought to further investigate the relationships between maternal language input, memory for false sentential complements, cognitive flexibility, and the development of explicit false belief understanding in 91 English speaking typically developing children and 30 children with specific language impairment. Concurrent and longitudinal findings converge in supporting a model in which maternal language input predicts the child's memory for false complements, which predicts cognitive flexibility, which in turn predicts explicit false belief understanding.

*Funders of the project: University of Western Australia Hackett postgraduate scholarship; University of Western Australia completion scholarship; NHMRC Program Grant #572742*

## LANGUAGE STABILITY AND CHANGE

CATE TAYLOR, DANIEL CHRISTENSEN, DAVID LAWRENCE, FRANCIS MITROU, STEPHEN R. ZUBRICK

Receptive vocabulary develops rapidly in early childhood and builds the foundation for

language acquisition and literacy. Variation in receptive vocabulary ability is associated with variation in children's school achievement, and low receptive vocabulary ability is a risk factor for under-achievement at school. This study looks at facilitators, prompts and constraints of receptive vocabulary development, as well as asking what normal development looks like.

A range of analytic techniques have been used in this study. Multivariate growth curve modelling was used to estimate trajectories of receptive vocabulary development in relation to a wide range of candidate child, maternal and family level influences on receptive vocabulary development from 4-8 years. Logistic regression has been used to assess risks, and to quantify how well early receptive vocabulary predicts subsequent performance.

Risks for receptive vocabulary delay at 4 years, in order of magnitude, were: Maternal Non-English Speaking Background (NESB), low school readiness, child not read to at home, four or more siblings, low family income, low birthweight, low maternal education, maternal mental health distress, low maternal parenting consistency, and high child temperament reactivity. None of these risks were associated with a lower rate of growth from 4-8 years. Instead, maternal NESB, low school readiness and maternal mental health distress were associated with a higher rate of growth, although not sufficient to close the receptive vocabulary gap for children with and without these risks at 8 years. SES area disadvantage was not a risk for low receptive vocabulary ability at 4 years but was the only risk associated with a lower rate of growth in receptive vocabulary ability. At 8 years, the gap between children

with and without SES area disadvantage was equivalent to eight months of receptive vocabulary growth. These results are consistent with other studies that have shown that social gradients in children's developmental outcomes increase over time.

Future work will look at the consequences of receptive vocabulary development for academic performance, as well as further assess the implications of our findings for policy and interventions.

*Project funding: NHMRC Program Grant #572742*

## FUTURE UNDER THREAT: CLIMATE CHANGE AND CHILDREN'S HEALTH

BRAD FARRANT, WITH FIONA ARMSTRONG AND GLENN ALBRECHT

Climate change has been widely recognised by leading public health organisations and prestigious peer reviewed journals as the biggest global health threat of the 21st century. Along with the old and disadvantaged, children are particularly vulnerable to the negative effects of climate change. Children suffer around 90% of the disease burden from climate change. Even if current international carbon reduction commitments are honoured, the global temperature rise is predicted to be more than double the internationally agreed target of 2°C. Humanity continues to pour record amounts of CO<sub>2</sub> into the atmosphere. It has been estimated that climate change will mean that Australian children will face a 30% to 100% increase across selected health risks by 2050. Indeed, if we fail to act, future generations of Australians may face a three- to 15-fold increase in these

health risks by 2100. We are only beginning to understand the impacts that climate change will have on children's physical and mental health. More research at the regional and local levels is desperately needed so we can adequately understand, prepare for and adapt to the impacts of climate change. The existence of cost effective ways to reduce climate change means there is no excuse for inaction. Climate change and the carbon-intensive energy system are currently costing 1.7% of global GDP and are expected to reach 3.5% by 2030. This is much higher than the cost of shifting to a low carbon economy. Right now the science is telling us that we are not doing enough. As children are innocent and non-consenting victims of climate change, adults have an ethical obligation to do everything possible to prevent further damage to their ability to thrive in the future. To do otherwise is to ignore the very thing many of us see as the most important reason for living.

## HUMAN DEVELOPMENT OF INDIGENOUS VERSUS NON-INDIGENOUS POPULATIONS IN DEVELOPED NATIONS

FRANCIS MITROU, DAVID LAWRENCE AND STEPHEN R. ZUBRICK, WITH MARTIN COOKE (UNIVERSITY OF WATERLOO), ERIC GUIMOND (DEPARTMENT OF ABORIGINAL AFFAIRS AND NORTHERN DEVELOPMENT CANADA), DAVID POVAH AND ELENA MOBILIA (BOTH OF THE AUSTRALIAN BUREAU OF STATISTICS)

Understanding the economics of Indigenous disadvantage is of particular importance if we are to lift Aboriginal children and families out of poverty and reduce over-representation in human services agencies in the foreseeable

future. We have a long-standing collaboration between The University of Waterloo (Canada), the Department of Aboriginal Affairs and Northern Development Canada, and the Australian Bureau of Statistics, to examine indicators of human development among Aboriginal populations in colonised Western nations. This includes plans for several papers over the next 3 years, the first of which uses a representative cohorts methodology to investigate changes in key socio-economic outcomes of Indigenous and non-Indigenous persons in three developed nations (Australia, Canada, and New Zealand) from 1981–2006.

*Funders of the project: NHMRC program grant #572742*

## Telethon Institute for Child Health Research (Adelaide Team) and the Fraser Mustard Centre

### OVERVIEW

At the Telethon Institute (Adelaide Team), a key component of the work includes the Australian Early Development Index (AEDI) research program, an Australian Government backed commitment that measures children's development in communities across the nation. The AEDI is a population measure of how our children develop through to their early school years. Teachers collect data across core areas of learning, health and wellbeing and this data is used to develop a snapshot of child development in communities across the nation.

Another aspect of the Adelaide Team is the

newly created "Fraser Mustard Centre". The Telethon Institute has joined forces with the SA Department for Education and Child Development to create a research partnership aimed at improving developmental, health and educational outcomes for children and young people. The Fraser Mustard Centre has been created to bring together leading Australian child researchers and innovative government policy makers and planners with a focus on enhancing programs and services for young people.

## RESEARCH AREA – DEVELOPMENT, EDUCATION, HEALTH AND WELLBEING OF CHILDREN AND YOUNG PEOPLE

### AUSTRALIAN EARLY DEVELOPMENT INDEX

SALLY BRINKMAN, TESS GREGORY

The Australian Early Development Index (AEDI) is a population measure of young children's development. Like a census, it involves collecting information to help create a snapshot of children's development in communities across Australia. Teachers complete the checklist for children in their first year of full-time schooling. The AEDI measures five developmental domains:

- Physical health and wellbeing
- Social competence
- Emotional maturity
- Language and cognitive skills (school-based)
- Communication skills and general knowledge

In 2009, the AEDI was completed nationwide for the first time with the Australian Government

providing \$21.9 million for the implementation of the AEDI in recognition of the need for all communities to have information about early childhood development. In 2009, information was collected on 261,203 children (97.5 per cent of the estimated national five-year-old population). In 2012, the second national census of child development was completed, and the results were released in April 2013. The second round of data collection involved 289,973 children (96.5 per cent of all children enrolled to begin school in 2012) and provided the first opportunity to explore change in the level of developmental vulnerability for children living in different communities, states and territories within Australia. The AEDI National Report 2012 shows that there has been a significant drop in the level of developmental vulnerability in Australian children from 23.6% in 2009 to 22.0% in 2012.

In 2011, the Australian Government Department of Education, Employment and Workplace Relations (DEEWR) awarded \$1.5 million in funding directly to TICHR to explore the 2009 and 2012 AEDI data and deliver on policy focused research. The research focuses on a range of questions pertinent to early childhood development such as:-

- Are there jurisdictional differences in the level of developmental vulnerability across Australia?
- Is there a differential impact of living in mining towns vs. non-mining towns for Aboriginal child development?
- How does the AEDI predict later academic outcomes during the primary school years?
- What is the best methodology to use to

determine whether communities, LGAs etc have experienced significant change in the childhood development from 2009 to 2012, and what is the best way to communicate this information to various stakeholders?

- How well do perinatal factors (e.g. low birth weight) predict childhood development at 5 years old?

Funder of the Project:

Commonwealth of Australia, Department of Education, Employment and Workplace Relations

*Acknowledgement:*

The Australian Government and State and Territory Governments are working in partnership with The Royal Children's Hospital Centre for Community Child Health in Melbourne, the Murdoch Childrens Research Institute, and the Telethon Institute for Child Health Research, Perth, to deliver the AEDI. The Social Research Centre, Melbourne, is managing the AEDI data.

## RANDOMISED CLUSTER CONTROL TRIAL EVALUATING THE IMPACT OF AN EARLY CHILDHOOD EDUCATION AND DEVELOPMENT INITIATIVE ACROSS INDONESIA

SALLY BRINKMAN, ANGELA KINNELL, MENNO PRADHAN, AMANDA BEATTY, AMELIA MAIKA, ELAN SATRIAWAN

With a greater scale for improvement in school readiness outcomes, the evaluation of early childhood education and development (ECED) programs in developing countries affords

a greater scope for investigation into the facilitators and barriers for success. This ECED program that we are evaluating represents a significant investment on behalf of the Republic of Indonesia and the World Bank.

It is estimated that up to half of Indonesia's population are vulnerable to poverty with the inequality between rich and poor vast. A large disparity in socio-economics, nutrition, education and health exist between districts, with infant and child mortality rates significantly higher in the poorer communities. In addition, children from the poorer villages start school later, complete fewer years of schooling and have higher drop out and repetition rates.

The objective of the ECED Project is to improve poor children's overall development and readiness for further education by (i) increasing the delivery of ECED services in targeted poor communities using a community-driven approach and (ii) developing a sustainable system for delivering ECED services. The project will reach approximately 738,000 children aged 0 to 6 and their parents/caregivers living in about 6,000 poor communities (dusuns) located in 3,000 villages within 50 districts.

The outcomes of the research will enable us: to determine (if and to) what extent the ECED Project improved children's development, attendance and readiness for school; to what extent the ECED Project improved parental awareness and practices; if the Project increased the availability and utilisation of ECED services and if so, how those impacts differed by gender, wealth, and level of service delivery at baseline. By including local academics in the research we will facilitate cultural relevance, local knowledge

and contextual relevance to the research (instrument development, fieldwork nuances through to identification of key stakeholders etc). A well designed and implemented impact evaluation will provide a unique opportunity to inform the current and future practices in Indonesia and abroad. In addition the evaluation will utilize outcome instrumentation that can be internationally referenced and thus rigorous piloting and cultural adaptation of internationally recognized instruments will be required.

The AusAID ADRA Grant has enabled the employment of two early career academics based at the University of Gadjah Mada (UGM) in Indonesia. As both academics are teaching university students, building their capacity, skills and knowledge will not only benefit themselves but their current and future students. Building local capacity will decrease the current reliance on "fly-in consultants" from Western countries.

*Funder of the Project: Australian Development Research Award (ADRA) awarded by AusAID*

## INDONESIAN EARLY CHILDHOOD EDUCATION AND DEVELOPMENT PROGRAM

SALLY BRINKMAN

Key Indonesian delegates (7 guests) from the World Bank and the Ministry of National Education working in the area of Early Childhood Education visited during October 2012 to learn about the South Australian and West Australian experiences of early childhood education programs and in implementing Australian Early Development Index (AEDI) as a measure of child development for further application in the

Indonesian context.

The delegates were put forward from both the World Bank and the Ministry of National Education and were people in senior operation roles, or which training and dissemination is part. They came to learn more about the new directions for early childhood and to inform early childhood and early education policies and practices in Indonesia.

Indonesian government is committed to expand access of quality Early Child Education and Development service, focusing on children (0-6) from poor families who benefit the most for their future education and life-long productivity. Quality of service is measured by its impact on child development. One well known indicator is the Australian Early Development Index (AEDI) of which the Australian government is strongest supporter. The AEDI was introduced in Indonesia through the impact evaluation of an on-going ECED program managed by Ministry of Education supported by the World Bank.

By exposing a group of Indonesian ECED leaders to AEDI, the program:

- developed a better understanding on the broad aspects that EDI is measuring
- understand the potential of using EDI for policy action, including management of public resources to improve access to quality ECED for the poor children
- understand the management aspect of implementing EDI (at national and sub-national level)

The overall aim was for the Indonesian Fellows to have hands on, real practical exposure to a variety of early childhood development

programs, early childhood education programs, programs linked and associated with schools, programs implemented by non-government agencies as well as community run programs. The programs were purposely diverse and operate in many of the poorer communities and/or communities with high diversity, as well as rural and metro based services/programs. The program also enabled the participants to have access to resources and manuals that could be easily adapted to the local Indonesian context.

Exposure and presentations were conducted by leaders in their fields here in Australia. These include leaders in both academia and also in government at a state and national level. The aim of presentations was to show how health and education and family and community services work together around not only Children's Centres but across government policy decisions to impact positively on child health, education and development.

The Australian program sought to build capacity and support around how ECED programs are implemented – using the Australian example and the monitoring of these programs as real and practical examples.

*Funder of the Project: Commonwealth of Australia, Australian Agency for International Development (AusAID)*

## THE FRASER MUSTARD CENTRE

DR SALLY BRINKMAN

The Fraser Mustard Centre is a new research collaboration between TICHR and the Department for Education and Children Development named in recognition of Dr Fraser

Mustard's contribution to South Australia.

This collaboration has been formed to provide new opportunities for evidence based policy decisions and partnerships based on a shared approach to child development. The collaboration is unique across Australia due to the degree of collaboration in its governance and activities. The Fraser Mustard Centre aims to:

- improve and promote the health and wellbeing of all children and young people in South Australia through the unique application of multidisciplinary research
- help shift focus from the historical delineation between health and education services to an integrated approach with a focus on 'child development'
- build capacity amongst public sector staff and academic researchers to design, undertake and use research to improve the environments in which children live and the service systems which support families
- attract research funding for shared priorities for research that leads to improved developmental, health, wellbeing and education outcomes for children.

The evaluation of the South Australian Children's Centres explained in more detail below is one of our primary projects, however in addition to this we are undertaking a variety of work including gender gap analyses. There is growing international evidence about the gap in educational outcomes between boys and girls. Although this trend appears to be evident in South Australian and national data, to date, little has been undertaken to document this trend and to understand the trajectories of boys as

compared with girls, identify the drivers of these developmental pathways and identify potential strategies for intervention. Thus, this project proposes to test whether there is a sufficient policy rationale for government to implement new strategies to respond to this issue and, if so, present options forward.

Another project is called Thriving in Adversity. Both NAPLAN and AEDI data reveal that although SES is a strong predictor of developmental and educational outcomes it is not destiny. Despite adversity in some low income communities there are individuals, schools and communities that are performing higher than would be predicted by the statistical models. This project seeks to explore the characteristics of these individuals, schools and communities that thrive in adversity to determine whether there are lessons to be learnt that may be transferable to other places.

One of the major initiatives of the Government's South Australian Youth Engagement Strategy and School Retention Action Plan is a program called the Innovative Community Action Networks (ICAN). Since its beginnings in 2003 ICAN has grown into a nationally recognised model of good practice in supporting young people who are enrolled in school but at risk of early leaving or becoming disengaged to a pathway to employment, further education or community participation. ICANs bring together young people, families, schools, community groups, businesses and different levels of government to find solutions to local issues that prevent young people from completing their education. As the program grows and matures it requires more sophisticated tools with which to measure its relative efficiency but more importantly the

means to measure the outcomes achieve for the young people it serves and what interventions work best for different sub populations. The Fraser Mustard Centre is working together with the Department to determine evaluation strategies.

## EVALUATION OF SOUTH AUSTRALIAN CHILDREN'S CENTRES

SALLY BRINKMAN, YASMIN-HARMAN SMITH

To reduce the impact of social inequality on children's outcomes, the South Australian Government has established a number of Children's Centres across South Australia. By the end of 2013, the Department for Education and Child Development will have established 34 Children's Centres. There will also be four Aboriginal Children's and Family Centres developed as a partnership between the State and Australian Governments. Children's Centres have been located in areas of high need to enable the provision of high quality services to children and families who may not otherwise have access to these supports. Children's Centres are based on a model of integrated practice, bringing together education, health, care, community development activities, and family support services in order to best meet the needs of vulnerable children and families.

Specifically, Children's Centres are tasked to provide universal services with targeted support in order to effect population outcomes in four areas: 1) Children have optimal health, development and learning; 2) Parents provide strong foundations for their children's healthy development and wellbeing; 3) Communities are child and family friendly; 4) Aboriginal

children are safe, healthy, culturally strong and confident (Department for Education and Child Development, 2011).

The Telethon Institute for Child Health Research through the Fraser Mustard Centre has been engaged to undertake a three year evaluation of these South Australian Children's Centres. The overall aims of the evaluation are to measure process and impact of integrated services in Children's Centres. The overall evaluation approach employs a mixed-method research design, employing qualitative and quantitative measures.

*Funder of the Project:*  
Government of South Australia, Department for Education and Child Development

## LOOKING AT LANGUAGE

MABEL RICE, CATE TAYLOR, STEPHEN ZUBRICK, SHELLEY SMITH.

This internationally unique study has been following the language development of more than 2000 WA children since 2002 and is the world's only study to conduct such detailed assessment of language and literacy development from infancy through the formative adolescent years. For the Institute, the ability to continue following the study children through early adolescence is ground-breaking. It is vitally important that we understand the developmental course of language and literacy from infancy and what different trajectories mean for young people's opportunities at school and beyond. Data collection for this project is based entirely in WA and involves 1000 families, 800 are families with twins.

In addition to formal language tests, researchers have collected genetic and environmental data as well as assessments with the study children's parents and siblings. A new innovation in the current funding period (2012 – 2017), will be to track children's pathways through school using Australia's National Assessment of Literacy and Numeracy (NAPLAN) data. The study will also provide previously unavailable insight into the increasing influence of social technology such as computers, mobile phones and the internet on language and learning in adolescence. LOOKING at Language is an international collaboration between Professor Mabel Rice from the University of Kansas, Professor Cate Taylor and Winthrop Professor Stephen Zubrick from the Telethon Institute for Child Health Research and The University of Western Australia and Professor Shelley Smith from the University of Nebraska Medical Center.

*Funders of the project:*  
USA National Institutes of Health (2002-2017)

## The Western Australian Pregnancy Cohort (Raine) Study

The Raine Study is one of the largest successful prospective cohorts of pregnancy, childhood, adolescence and now young adulthood in the world and a unique resource for local, national and international researchers. 80% of the original participants are still active and committed to the project. Each member of the cohort has over 85,000 measures of health and disease and information on more than 2.5 million genetic variants. The Raine Study began in 1989 at King Edward Memorial Hospital with the recruitment of 2900 pregnant women in

early pregnancy in a research project assessing ultrasound examination. These families were followed through pregnancy and 2868 children born to the mothers were recruited into the Raine cohort. Since birth, the cohort participants been reviewed in detail on eleven occasions at ages 1, 2, 3, 5, 8, 10, 14, 17, 18, 20 and now at 23 years of age.

The Raine Study is governed by the Raine Study Executive Committee and managed by the Scientific Directors and Raine Study Manager. There are 25 collaborative expert groups under the leadership of a Principal Investigator, which include Anaesthesia, Asthma & Allergy, Cardiovascular & Metabolic, Cognitive Neuroscience, Dental Health, Developmental Origins of Health and Disease, Eating Disorders, Endocrinology, Epigenetics, Gastrointestinal & Hepatology, Genetic Epidemiology, Growth, Hypothalamic-Pituitary-Axis, Infectious Disease, Language Development, Mental Health, Musculoskeletal, Nutrition, Ophthalmology, Otolaryngology, Physical Activity, Pregnancy & Birth, Reproductive Health, Risk Taking Behaviour and Sleep.

2012 was a busy and productive year for Raine Study management, the Raine Study Team, researchers and cohort participants. The 20 year old cohort review was completed in March 2012, and simultaneously the 23 year old assessment started. A total of 55 research papers were published in peer reviewed journals in 2012.

The fifth Raine Study Annual Scientific Meeting was held on Friday 17 August 2012 at the UWA Club. The Event was opened by His Excellency the Governor and Mrs McCusker. Over 100 Raine Study Researchers attended the meeting and

participated in over 20 presentations. The Raine Medical Research Foundation kindly donated prizes for the Best Presentations by a young researcher. These were awarded to students Lauren Hollier and Bianca Petterson.

The Raine Study Core Management provide top up PhD scholarships for Raine Study PhD students. In 2012 top-up scholarships were awarded to PhD candidates Dr Chi le Ha and Dr Anett Nyaradi.

The Raine Medical Research Foundation generously supports the position of the Raine Study Scientific Director. In late 2012, after five years in the position Associate Professor Craig Pennell resigned as Raine Study Scientific Director. Under his leadership the Raine Study has flourished and developed with increased collaborative research between researchers - locally, nationally and internationally, with increased success in attracting grant funding and with increased productivity. In December 2012, the Executive Committee announced that Professor Peter Eastwood accepted the position of Raine Study Scientific Director and Professor Leon Straker accepted the position of Associate Raine Study Scientific Director.

## LONGITUDINAL COHORT STUDIES

### THE RAINE STUDY 20 YEAR FOLLOW UP - THE OPHTHALMIC FOLLOW-UP STUDY OF A LONGITUDINAL BIRTH COHORT AT AGE 20/21 YEARS

PROFESSOR DAVID MACKAY, DR ALEX HEWITT, DR ALLA SOLOSHENKO, SANDRA OATES, SEYAN YAZAR, DR ALEX TAN, DR HANNAH FORWARD, DR CHARLOTTE MCKNIGHT, ASSOC PROF CRAIG

### PENNEL, JENNY MOUNTAIN, RAINE STUDY TEAM

The 20 year cohort follow up started in March 2010 and was completed in April 2012. Over 1350 Raine Study Participants came to the Lions Eye Institute and underwent 27 eye test procedures. Participants also had a DEXA scan, a liver fibroscan, completed questionnaires and had a physical assessment which include height, weight, anthropometry and blood pressure. They also provided a blood sample. Participants were given the results of their eye tests and DEXA scan on the day of testing. Data from the the eye examination will be linked to genetic data to determine genes associated with particular eye measurements and disease.

Funders of the project: NH&MRC 1021105, 634445, 634457, 634509, 1003424, Canadian Institute of Health Research \_MOP 82893, Raine Study Core Management Funding, Australian Foundation for the Prevention of Blindness, Lions Eye Institute, Alcon Research Institute

### THE RAINE STUDY 20 YEAR FOLLOW UP - DEXA SCAN OF THE RAINE COHORT

ASSOC PROF CRAIG PENNELL, PROF STEPHEN LYE, PROF LEON STRAKER, DR KATHY ZHU, JENNY MOUNTAIN, RAINE STUDY TEAM

During the 20 year cohort follow up 608 females and 670 males had a DEXA scan. The DEXA scan provides measures of body composition (lean mass, fat mass, bone mass) as well as bone density and is considered the 'gold' standard measurement of adiposity. An optimal peak bone mass is considered the best protection against age-related bone loss and subsequent

fracture risk. Peak total body bone mass is generally attained by 20 years of age. Worldwide there are limited data available on the lean and fat mass and peak bone mass in young adults. These measurements will contribute significantly to research on relationships between lean body mass, fat mass and bone mass in young adults and the factors that influence and modify them.

*Funders of the project:*  
Canadian Institute of Health Research CIHR (Lye et al, MOP 82893)

*DXA machine: Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital.*

### THE RAINE STUDY 20 YEAR FOLLOW UP - FIBROSCAN IN THE RAINE COHORT

DR ENG GAN, PROF LEON ADAMS, PROF JOHN OLYNYK, PROF LAWRIE BEILIN, ASSOC PROF CRAIG PENNELL, PROF WENDY ODDY, DR OYEKOYA AYONRINDE, RAINE STUDY TEAM

The prevalence of Non-alcoholic fatty liver disease (NAFLD) in the Raine cohort at 17 years was 13%, placing these subjects at possible risk of further complications. The Raine Study participants had a Fibroscan at the 20 year follow up to measure liver stiffness. The Fibroscan is a new technology where a probe is placed on the skin where the liver is situated and a mechanical pulse used to measure liver stiffness. It is non-invasive and rapid (previously a liver biopsy was required to assess fibrosis or liver scarring). The measurements taken on the Raine Study Cohort will establish the norms for Fibroscan results in this age group. 1241 Raine Study participants underwent a Fibroscan. Males

had a slightly higher liver stiffness than females, 4% of the participants had measurements outside the normal range and liver stiffness was associated with obesity, high blood pressure and excessive alcohol intake.

*Funders of the project: NH&MRC 634445*

### THE RAINE STUDY 20 YEAR FOLLOW UP - THE EARLY LIFE ORIGINS OF IMPAIRED TESTICULAR FUNCTION

PROF ROGER HART, PROF MARTHA HICKEY, PROFESSOR NIELS SKAKEBAEK, DR STEPHEN JUNK, ASSOC PROFESSOR DOROTA DOHERTY, MICHELLE PEDRETTI, ALEX D'VAUZ, RAINE STUDY TEAM

Over the last few years there have been reports that male sperm counts are decreasing and that this is beginning to be evident at a younger age. Many of these findings are based on sperm counts from people seeking infertility treatment and not from healthy groups. It is not known why some people have low sperm counts although there is some evidence suggesting that smoking, obesity and factors in environment can affect sperm count. As a population we are being exposed to increasing amounts of chemicals in the environment (endocrine disrupters) which may affect sperm production. The Raine Male Fertility Study is a world first. Over 400 males participated in the study, representing 60% of those who did the 20 year follow up. Participants who had results below normal ranges were referred to a specialist. Those who had the best sperm samples generally had a healthy lifestyle and had not been exposed to cigarette smoke. Further analyses are being conducted to determine what factors affect fertility in young

men.

*Funders of the project: NH&MRC 634457.*

## THE RAINE STUDY 23 YEAR OLD FOLLOW UP - THE EVOLUTION OF CHILDHOOD OBESITY AND ITS RELATIONSHIP TO ADULT SLEEP DISORDERED BREATHING

PROF PETER EASTWOOD, PROF DAVID HILLMAN, DR ANNE SMITH, DR NIGEL MCARDLE, ASSOC PROF RAE CHI HUANG, STUART MACGREGOR, JENNY MOUNTAIN, DIANE WOOD, RAINE STUDY TEAM, RAINE SLEEP TECHNOLOGY TEAM.

A major focus of the 23 year Raine Study assessment is sleep. Sleep affects all aspects of physical and mental well-being but almost nothing is known about the characteristics of sleep in young adults. The follow up of the Raine cohort at 23 years of age started in March 2012. Participants are invited to spend the night in the Centre for Sleep Science (CSS) at the University of Western Australia and have a polysomnograph (Sleep Study). This study will utilise the longitudinal data collected on children and their families to determine, for the first time, the prevalence, clinical picture and risk factors for obstructive sleep apnea (OSA) and other sleep disorders in early adulthood. The specific aims of the study are to determine the prevalence of OSA syndrome in early adulthood; to characterise and establish the risk factors for OSA in young adults and identify early life predictors (including developmental, social, environmental and biological characteristics) associated with the development of OSA in young adults.

The participants also undergo other physical measurements and complete questionnaires. At the end of 2012 over 400 Raine Study Participants had completed a sleep study. This has been an amazing achievement involving sleep technologists, Raine Study staff, students, respiratory physiologists and other expert researchers.

*Funders of the project: NH&MRC 1027449, Raine Study Core Management Funding*

## THE RAINE STUDY 23 YEAR OLD FOLLOW UP - TRANSITION FROM CHILDHOOD TO ADULT ASTHMA: PREDICTING PERSISTENT AND ADULT-ONSET ASTHMA IN YOUNG ADULTS IN THE RAINE LONGITUDINAL BIRTH COHORT.

PROF GRAHAM HALL, PROF PAT HOLT, DR ELYSIA HOLLAMS, PROF ZOLTAN HANTOS, PROF PETER SLY, PROF ALAN JAMES, PROF CRAIG PENNELL, ELISHA WHITE, DR CLARA FOO, JENNY MOUNTAIN, DIANE WOOD, RAINE STUDY TEAM

The causes and development of asthma and related diseases is a key research program within the Raine Study. The Raine Study is one of the largest studies measuring lung function and bronchial responsiveness in preschool aged children. Major respiratory assessments were undertaken at birth, 6 and 14 years of age and findings led to early intervention trials targeting risk factors with the aim of preventing the development of asthma during childhood. The transition between the child and adult forms of asthma is a crucial research issue and doing a comprehensive respiratory assessment in the Raine Study cohort at age 23 provides

a unique opportunity to track asthma status and development over 23 years. The primary objective of this project is to characterise the asthma-related clinical characteristics and associated immunophenotypes that persist beyond adolescence into early adulthood and to establish a baseline for the continuing study of chronic respiratory diseases in later life.

During the 23 year assessment, participants have a lung function test and an allergy skin prick test before settling into bed to be set up for the sleep study. In the morning, they have an assessment of airway hyper-responsiveness and further lung function testing. During 2012 over 400 Raine Study participants completed the respiratory assessment.

*Funders of the project: NH&MRC 1021858, Raine Study Core Management Funding*

## THE RAINE STUDY 23 YEAR OLD FOLLOW UP - A LIFE COURSE APPROACH TO CHARACTERISING AND PREDICTING INACTIVITY AND SEDENTARY BEHAVIOUR OF YOUNG ADULTS INCLUDING RELATED WORKLOSS

PROFESSOR LEON STRAKER, DR ANNE SMITH, ROB WALLER, ANNEGRET HARRIES, REBECCA NGUYEN, THALIA BOTSIS, RAINE STUDY TEAM

Sedentary behaviour has been shown to be an independent risk factor for obesity, diabetes, cardiovascular disease and some cancers. Raine Study participants are fitted with ActiGraph accelerometers which are used to record all light, moderate and vigorous physical activity, sleep activity and sedentary behaviour. The accelerometers are worn continuously on the

left wrist and right hip on the night of their sleep study and for the next 7 days and participants keep a brief log documenting their activity.

Quantitative Sensory Testing is measured by assessing the pressure pain threshold and the cold pain threshold. This is the first time that QST is being assessed a young adult cohort and these measures will be used assessing risk of chronic pain for when assessing work productivity and work loss.

Work loss due to work absenteeism or presenteeism (where a person is at work but not fully functional through illness or tiredness) creates a substantial burden on society. Health is an important reason for absenteeism and presenteeism. Work loss is being assessed using the World Health Organisation measures and is being done through the use of web based technology and smart phones.

*Funders of the project: NH&MRC 1044840, Safe Work Australia, Raine Study Core Management Funding*

## RAINE STUDY: CHILD AND ADOLESCENT EATING DISORDERS

### EATING DISORDERS IN WESTERN AUSTRALIA: PREVALENCE, MAINTAINING FACTORS AND PROSPECTIVE RISK FACTORS

KARINA ALLEN, SUE BYRNE, WENDY ODDY.

This 4-year project commenced in June 2010 and has a central focus on the development, persistence, and consequences of eating

disorders in adolescence. The research utilises data from the Western Australian Pregnancy Cohort (Raine) Study. Eating disorder symptoms were assessed at the 14, 17, and 20-year Raine Study follow-ups.

Data from the 20-year Raine Study follow-up became available in 2012. The focus over the last year has therefore been on analysing the three available waves of eating disorder data (ages 14, 17 and 20) to identify (i) changes in the prevalence of eating disorders over time; (ii) predictors of eating disorder persistence across adolescence; and (iii) 20-year outcomes for adolescents who experienced persisting eating disorder symptoms across their adolescent years.

We found that the prevalence of full and partial eating disorders in the Raine Study cohort increased from approximately 6% at age 14 to approximately 9% at ages 17 and 20. Of the adolescents with an eating disorder at age 14, approximately half continued to report significant eating pathology six years later. Acting out behaviour (e.g., rule-breaking) in early adolescence and purging (self-induced vomiting or laxative misuse) in middle adolescence were the strongest predictors of an eating disorder persisting across adolescence. Participants who reported persisting eating disorder symptoms also reported significant and persisting problems with depression and anxiety.

We have also considered the trajectory of individual eating disorder symptoms, such as binge eating, purging and fasting (not eating for >8 hours to control weight). Female Raine Study participants experienced marked increases in eating disorder symptoms, on average, between

ages 14 and 17: purging increased from 4% to 14% and fasting increased from 16% to 26%. Symptoms remained high at age 20. Fewer changes over time were observed for boys, but depression in early adolescence was associated with higher rates of eating disorder symptoms in both boys and girls.

The last year allowed us to explore possible early life risk factors for eating disorders. We found a relationship between low maternal vitamin D levels at 18 weeks gestation and increased risk for an eating disorder in female offspring by age 20 years. These findings are novel and extend previous research on season of birth (which correlates with gestational vitamin D levels) and eating disorder risk in later life.

We have consistently found low rates of treatment seeking amongst Raine Study participants identified as meeting criteria for an eating disorder. Even amongst participants who met criteria for an eating disorder at 14, 17 and 20 years, only 20% reported being diagnosed with, or treated for, an eating disorder by age 20 years. To address this, we are developing a project that aims to identify barriers to help-seeking for eating disorders and related mental health problems in adolescence. This research will run separately to the Raine Study, by collecting questionnaire data from high school students in the Perth metropolitan region.

*Funders of the project: National Health and Medical Research Council (NHMRC) Early Career Research Fellowship - Karina Allen. University of Western Australia Early Career Researcher Fellowship Support grant - Karina Allen.*

## Social determinants of child health/social epidemiology

### PARENTAL WORK HOURS AND QUALITY OF DIET IN ADOLESCENTS

JIANGHONG LI, WENDY ODDY, THERESE O'SULLIVAN, SARAH JOHNSON

The study investigates the association of mother's and fathers' work hours and other socioeconomic factors with diet quality in a cohort of adolescents followed from pregnancy to age 13 in Western Australia (the Raine Study), using a diet quality index and dietary patterns developed at the Institute for Child Health Research.

*Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.*

This work has now been published in *Public Health Nutrition*

Jianghong Li, Therese O'Sullivan, Sarah Johnson, Fiona Stanley, Wendy Oddy. Maternal work hours in early to middle childhood link to later adolescent diet quality. *Public Health Nutrition* (accepted 25 October 2011: published online first: [http://journals.cambridge.org/repo\\_A84ow7rn](http://journals.cambridge.org/repo_A84ow7rn)).

### PARENTAL WORK AND CHILD HEALTH AND DEVELOPMENT

JIANGHONG LI, GARTH KENDALL, LYNDALL STRAZDINS, MIKE DOCKERY, SONIA ANDREWS, SARAH JOHNSON, RACHEL SKINNER, WEN-JUI HAN (THE US).

The project aims to investigate the impact of parental employment status and non-standard work schedules on the health and wellbeing of Australian children/adolescents and to shed new light on the social and economic causes of the high prevalence of mental health problems in today's children. The proposed research will be based on data from Longitudinal Study of Australian Children (LSAC) and the Western Australian Pregnancy Cohort Study (Raine). The project draws on multidisciplinary expertise from sociology, social epidemiology, developmental epidemiology, clinical psychology and labour economy. We have conducted a comprehensive review of the literature on non-standard work schedule and child mental health and behavioural problems and the review will inform specific research aims and questions.

This program of research investigates the following outcomes: Mental health, risk taking behaviours, body mass index, and school achievement.

*Funders of the project: Projects undertaken by Dr Jianghong Li and supported by The Foundation for Children and her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.*

### MATERNAL STRESSFUL EVENTS IN PREGNANCY AND NUMERACY AND LITERACY AT GRADE 5

JIANGHONG LI, MONIQUE ROBINSON, ANKE VAN EEKELLEN, JONATHAN FOSTER, EVA MALACOVA.

This study examines the timing and number of stressful events in pregnancy and their link with



numeracy and literacy achievement in a subset of the Raine Cohort children in grade 5 who attended government schools in WA. The aim of the study is also to demonstrate the importance of examining gender difference in the impact of maternal stressful events in pregnancy on offspring's school achievement and to elucidate the need to distinguish between confounding factors from mediating factors in the causal pathway.

*Funders of the project:*

*Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.*

This work has resulted in a journal article currently under revision for resubmission to Journal of Pediatrics in April 2012.

## HIV VULNERABILITY IN OUT-OF-SCHOOL ADOLESCENTS AND YOUTH IN YUNNAN, CHINA

LIJUN YANG (CHINA), JIANGHONG LI.

This is a UNICEF funded project based in China and I am a collaborator on the project. The project aims to understand the level of knowledge about HIV transmission and prevention and risk taking behaviours in a random sample of out-of-school adolescents in Yunnan Province. Cross-sectional data has been collected and the project is at the stage of analysis.

*Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation*

*Research Institute, Centre for Developmental Health, Curtin University.*

This work has been accepted for publication in *World Journal of AIDS* (5th April 2012):

Jianghong Li, Lijun Yang, Zhouyang Ren, Chongbin Mo, Dingwen Chen, Fuqiang Dai, Mingzhong Jiang, Zhijie Tang, Peter Jacoby. HIV Vulnerability in out-of school adolescents and youth in Yunnan, China. *World Journal of AIDS* (accepted 5th April 2012).

## HOUSING AND CHILDREN'S HEALTH AND DEVELOPMENT

M DOCKERY, G KENDALL, J LI, L STRAZDINS, F CHAN, R ONG, R SEYMOUR, A MAHENDRAN

This is a scoping study that provides a review of international research literature on the link between housing and children's health and development and it proposes a research plan for developing this area of research in Australia. Further funding has been obtained from Australian Housing and Urban Research Institute to carry out the research plan in 2011 and beyond. The project will investigate the effect of housing location and housing quality and ownership on child developmental outcomes.

*Funders of the project: Australian Housing and Urban Research Institute*

On going

## DETERMINANTS OF CHILD POVERTY IN THE US

JIANGHONG LI, JOACHIM SINGELMANN (THE US).

The proposed project will build on the analyses

of family poverty in the Mississippi Delta and the Texas Borderland recently carried out by Singelmann and his associates. A key finding of their research has been the importance of poverty-intervention programs that target specific socio-demographic groups. Their results show that the correlates of poverty differ among race and ethnic groups as well as among family types (both parent vs. single parent). The proposed project will extend these analyses to the third high-poverty region in the United States, which is Central Appalachia. All three regions have a poverty rate exceeding 20%. The focus of the proposed project will be on the determinants of child poverty and differences in these determinants by race, ethnicity and household type. By focusing on the three poverty regions mentioned above, such race/ethnic differentiation will be possible, given the high concentration of blacks in the Delta and of Latinos in the Borderland.

*Funders of the project: Projects undertaken by Dr Jianghong Li and supported by The US Studies Centre at the University of Sydney and her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.*

This project has been completed and a final report submitted to the funder in April 2012.

## RAINE STUDY: NUTRITION GROUP

PROFESSOR WENDY ODDY, DR GINA AMBROSINI, DR THERESE O'SULLIVAN, DR MONIQUE ROBINSON, DR LUCINDA BLACK, DR GEORGINA TRAPP, DR ANETT NYARADI, MS CARLY HERBISON, MS CAROLINE GALLAGHER

Cardiometabolic (obesity, cardiovascular disease,

type 2 diabetes, liver injury) and mental health disorders are of increasing population health concern for Australia as well as globally. The primary aim of the nutrition team is to describe relationships between nutritional factors, cardiometabolic and mental health disorders from infancy to adulthood. A wide range of data have been collected in the Raine Study during pregnancy, at birth (n=2868), and at 1, 2, 3, 6, 8, 10, 14 and 17 years of age. The 20 year follow-up is almost complete. Existing and newly collected data is being used by the Nutrition team and replication of findings are being reported in collaboration with the Avon Longitudinal Study of Parents and Children (ALSPAC) study in Bristol. The Raine study is ideally placed for a life-course approach in cardiometabolic and mental health disorders. By examining these trajectories to 20 years of age we can identify early determinants of risk and key times for intervention.

**In 2012 the Nutrition Team was involved in the projects listed below:**

## DIETARY PATTERNS AND FATTY LIVER DISEASE

WENDY ODDY, CARLY HERBISON, PETER JACOBY, GINA AMBROSINI, THERESE O'SULLIVAN, OYEKOYA AYONRINDE, JOHN OLYNK, LUCINDA BLACK, LAWRIE BEILIN, TREVOR MORI, BETH HANDS, LEON ADAMS.

Objective: Poor dietary habits have been implicated in the development of non-alcoholic fatty liver disease (NAFLD); however, little is known about the role of specific dietary patterns in the development of NAFLD. We examined prospective associations between dietary patterns and NAFLD in a population-based cohort of adolescents.

Method: Participants in the Western Australian Pregnancy Cohort (Raine) Study completed a food frequency questionnaire at 14 years and had liver ultrasound at 17 years (n = 995). Healthy and Western dietary patterns were identified using factor analysis and all participants received a z score for these patterns. Prospective associations between the dietary pattern scores and risk of NAFLD were analysed using multiple logistic regression.

Results: NAFLD was present in 15.2% of adolescents. A higher Western dietary pattern score at 14 years was associated with a greater risk of NAFLD at 17 years (OR 1.59; 95% CI 1.17,2.14; p < 0.005), although these associations were no longer significant after adjusting for body mass index at 14 years. However, a healthy dietary pattern at 14 years appeared protective against NAFLD at 17 years in centrally obese adolescents (OR 0.63, 95% CI 0.41, 0.96; p = 0.033), whilst a Western dietary pattern was associated with increased risk of NAFLD. Conclusions: A Western dietary pattern at 14 years was associated with increased risk of NAFLD at 17 years, particularly in obese adolescents. In centrally obese adolescents, a healthy dietary pattern may protect against NAFLD, while a Western dietary pattern may increase the risk of NAFLD.

*Funders of the project: NHMRC grants #353514, 403981 and 634445, the Commonwealth Scientific and Industrial Research Organisation and the Australian Heart Foundation / Beyond Blue Strategic Research Initiative (ID G08P4036).*

## EARLY INFANT FEEDING AND LONG-TERM METABOLIC HEALTH

WENDY ODDY, RAE-CHI HUANG, TREVOR MORI, CARLY HERBISON, MEG MCHUGH, BERTHOLD KOLETZKO, LAWRENCE BEILIN.

This project investigates whether a shorter duration of breastfeeding may be associated with an increased risk of the metabolic syndrome in the long-term later in adolescence. Our objective was to investigate associations between early infant feeding and prevalence of the metabolic syndrome at 17 years as defined by a high-risk metabolic cluster identified in a prospective pregnancy cohort. Infant feeding history was assessed by questionnaire in 2420 children at one year of age participating in The Western Australian Pregnancy Cohort (Raine) Study. Metabolic syndrome was identified at 17 years using a population-derived “high-risk” metabolic cluster variable. We showed that metabolic syndrome prevalence was 17% as classified by the high-risk metabolic cluster. Breastfeeding cessation prior to two months of age was associated with an increased prevalence of the metabolic syndrome at 17 years p<0.05. In addition, breastfeeding cessation before two months was associated with high waist circumference as defined by being in the high-risk metabolic cluster (OR 1.43; 95% CI: 1.12-1.82). We concluded from this study supports that a shorter duration of breastfeeding is associated with a higher prevalence of the metabolic syndrome in adolescence.

*Funders of the project: Heart Foundation/ Beyond Blue Strategic Research Initiative grant.*

*NH&MRC 403981 and NHMRC-EU collaborative project 1037960 (funded for five years 2012-2016).*

This research has received funding from

the European Union’s Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement n°289346.

## NUTRITIONAL DETERMINANTS OF CARDIO-METABOLIC AND MENTAL HEALTH RISK

WENDY ODDY, THERESE O’SULLIVAN, RAE-CHI HUANG, TREVOR MORI, GINA AMBROSINI, PETER JACOBY, CARLY HERBISON, MEG MCHUGH, LEON ADAMS, LAWRENCE BEILIN, GINA TRAPP, LUCINDA BLACK, CAROLINE GALLAGHER.

Cardio-metabolic and mental health disorders are of increasing population health concern for Australia as well as globally. The primary aim of this project is to describe relationships between nutritional factors, cardio-metabolic and mental health disorders from infancy to adulthood. A wide range of data have been collected in the Raine Study during pregnancy, at birth (n=2868), and at 1, 2, 3, 6, 8, 10, 14 17 and 20 years of age. Existing and newly collected data are being used and replication of findings are being reported in collaboration with the Avon Longitudinal Study of Parents and Children (ALSPAC) study in Bristol. The Raine study is ideally placed for a life-course approach in cardio-metabolic and mental health disorders. By examining these trajectories to 20 years of age we can identify early determinants of risk and key times for intervention.

*NH&MRC 1022134 (funded for three years 2012-2014).*

## NUTRITIONAL DETERMINANTS OF COGNITIVE DEVELOPMENT

## HEAD OF DIVISION

ANETT NYARADI, WENDY ODDY, SIOBHAN HICKLING, JIANGHONG LI, JONATHAN FOSTER, ANDREW WHITEHOUSE.

In this PhD project Dr Anett Nyaradi is investigating relationships between dietary intake and cognitive and educational performance in a cohort of Western Australian children to 17 years, and contribute to a growing body of knowledge concerning diet, cognitive development (as measured by CogState) and educational outcome.

The specific aims of the project are to:

1. Conduct a comprehensive literature review on diet, cognitive development and educational outcome.
2. Investigate the relationship between early dietary intake as a diet quality score and specific food group scores (years 1, 2 and 3) and cognitive outcome in childhood (years 5, 8 and 10).
3. Examine the relationship between early childhood diet as a diet quality score and specific food group scores (years 1, 2 and 3) and cognitive development (as measured by CogState) in adolescents at age 14 and 17.
4. Investigate the relationship between adolescent diet quality (years 14 and 17) and CogState (years 14 and 17).
5. Investigate the relationship between specific food groups, nutrients and academic achievement of 14 years old adolescents.

*Dr Nyaradi has received a UWA APA scholarship*

and a Raine Study scholarship to conduct this PhD Project.

## Childhood Obesity

### INVESTIGATING METHODS FOR MANAGING CHILDHOOD OBESITY

LISA GIBSON

Currently there are no satisfactory treatment or prevention strategies for overweight and obese children. New treatment approaches to the management of childhood obesity are needed. This project aims to develop, test and disseminate a new intervention for childhood obesity. Our evidence-based Healthy Eating and Lifestyle Program (HELP) applies cognitive behavioural principles to the problem, focusing on the mother's role in her child's weight management. It targets overweight or obese mothers with overweight or obese children using a group format with mothers who attend 10 weekly sessions. The underpinning logic of the program is that if mothers are better equipped to manage their own weight, they will subsequently be more able to do so in the context of the whole family.

Underpinning the focus on mothers are data from the Western Australian (WA) Childhood Growth and Development Study. These data indicate that a mother's body mass index (BMI) was the strongest predictor of her child's BMI. Further, more than 80% of children in the study who were overweight or obese had mothers who were also overweight or obese. This is not altogether surprising given that mothers are key role models for their children's dietary and exercise behaviour and play an influential role in the areas of cognition and emotion in the areas

of eating and weight.

On three occasions, between 2009-2011, HELP was offered as a free program to families living in a southern metropolitan area of WA. Saturation advertising and promotional methods were used to recruit families. Typically, this involved two weeks of paid advertising along with editorial coverage of HELP in a community newspaper, although on one occasion, an article about the program also appeared in the State's major daily newspaper. On each occasion, program information was sent to local primary schools for inclusion in school newsletters and advertising flyers were displayed around the local government area in places like schools, shopping centres, medical centres, child health clinics, playgroups, libraries and community centres. Other promotional avenues included a Facebook page, paid advertising through Facebook, and participation in a talk back radio program that discussed issues within the local area. On one occasion we also advertised a community forum to find out why the first attempt to recruit families to HELP was unsuccessful. This forum was subsequently cancelled due to lack of community interest.

The promotion of the program also entailed a partnership with community health workers and local government officers, giving emphasis to their potential contribution with recruitment and in providing practical support for local delivery of HELP sessions. Although poorly attended, we also ran community forums to introduce HELP and its facilitator to the community prior to program commencement.

Despite this substantial effort to market our

program, the response was minimal with only a handful of people ever making email or phone inquiries about participating. Consequently, we have been unable to deliver the 10 session HELP program.

This outcome surprised and puzzled us, not least because of the high prevalence of overweight and obesity in both adults and children and the almost daily expressions of concern about these issues in the popular media.

In an attempt to find out why we weren't able to enlist families in the program, we conducted two focus groups with nine local community health workers and surveyed parents of primary school children in the area. The response to the parent questionnaire was also poor, with only 50 questionnaires returned (a 2% response rate). Several themes emerged from this research, shedding some light on possible reasons for our lack of recruitment success. The first of these was the issue of mothers being "time poor", as they attempt to balance home, work and other commitments.

However, the subsequent reasons suggest that many mothers might avoid programs that deal with the issue of overweight and obesity within their family because they associate them with both substantial difficulty with respect to managing dietary change in the family and an unacceptable level of exposure to personal or family level stigma.

This research reinforces the point that having an evidence-based intervention is only part of the solution to addressing childhood obesity. Second, it highlights that we know far too little about how we might encourage time poor

mothers to embark on a journey of personal and family level behaviour change that they may find threatening and difficult. Despite the daunting challenge of addressing this, the health costs of failing to find effective strategies appear unacceptable. Future work will focus on identifying strategies to overcome these barriers and to ensure participation in future intervention programs.

*Funders of the project: Western Australian Health Promotion Foundation (Healthway).*

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Dr Rochelle Watkins BSc (Physio), PhD, GradDipMgnt  
Linda Watson  
Dr Andrew Whitehouse, BSc (Human Communication Science), PhD  
Dr Amanda Wilkins MBBS, FRACP, MPH  
Catherine Wilson  
Kathryn Wilson  
Kingsley Wong, MBBS MBA MSc AFCHSM, MPH candidate, UWA  
Dianne Wood, BAppSc(Phys Ed)Dip Ed, Grad Dip HN  
Stephanie Yeong

## RESEARCH SUPPORT STAFF

Claire Fowler  
Colette Newcomb  
Leanne Scott

## POSTGRADUATE STUDENTS

Alison Anderson, BSc (Hons), GradDipPH, PhD candidate, UWA  
Jaimi Andrews, Honours candidate, ECU  
Oyekoya Ayonrinde, PhD candidate, UWA  
Katherine Bathgate, BSc (Nutr & Food Sc), Grad Dip Diet, Grad Cert Teach, MPH, APD, PhD

candidate, Curtin  
Dr Sunil Bhat, Masters of Public Health candidate, UWA  
Jenna Blumberg, PhD candidate, UWA  
Katrina Boterhoven de Haan, BPsych (Hons), Enrolled in MAppPsych (Clinical)  
Sally Brinkman, BA, MPH, PhD candidate, Curtin  
Katerina Chin-A-Loy Lima, PhD candidate, UWA  
Daniel Christensen, BA Psych (Hons), Enrolled in MSc (Applied Statistics)  
Lyn Colvin, PhD candidate, UWA  
Denise Demmer BSc (Hons), PhD Candidate  
Aditya Deshpande, BDS, PhD candidate, UWA  
Jenny Fairthorne, BA, Dip Ed., MSc, MPH, PhD candidate, UWA  
Stephanie Fehr, BSc, BMedSci (Hons), PhD candidate, UWA  
Simone Fernandez, PhD candidate, UWA  
Anna Ferrante BA (Mathematics), Dip Ed, PhD candidate  
Kitty-Rose Foley, BSc (OT) (Hons), PhD candidate, ECU

Dr Hannah Forward MBBS Masters Candidate  
Dr Eng Gan MBBS, PhD Candidate  
Tegan Grace BSc (Hons), PhD Candidate  
Noula Gibson, BAppSc(Physio)(Hons), M Physio(Develop Paeds), PhD candidate, UWA  
Katherine Hafekost, Enrolled in MSc (Applied Statistics)

Michèle Hansen, MPH, BSc, PhD candidate, UWA  
Aveni Haynes, Masters/PhD candidate, UWA  
Carly Herbison, PhD candidate, UWA  
Lauren Hollier, PhD candidate, UWA  
Katrina Hopkins, BAppSci(Psych), DipEd(Psych),  
MAppSci(Health Sciences), PhD candidate, UWA  
Nan Hu, MSc, PhD candidate, UWA  
Milena Jacobs, PhD candidate, UWA  
Amanda Jefferson, BSc, PhD candidate, Curtin  
Christine Jeffries-Stokes, MBBS, MPH, PhD  
candidate, UWA  
Jocelyn Jones, BA (Sociology), EN, MAE, PhD  
candidate, UWA  
Rachel Jones, Honours candidate, UWA  
Brilliana von Katterfeld BA BSc(Hons) PhD  
candidate, UWA  
Dr Chi Le-Ha MBBS, PhD Candidate  
Wendy Lim, BMedSci Candidate  
Sandra Louise, PhD candidate, UWA  
Miriam Maclean, PhD candidate, UWA  
Dr Richard Maganga MBBS, PhD Candidate  
Geraldine Maibani-Michie, PhD candidate, Curtin  
Caitlin Marr, Post Grad Diploma candidate,  
Curtin  
Julie Marsh BSc MSc, PhD Candidate  
Dr Charlotte McKnight MBBS Masters Candidate  
Mary-Ann Measey, PhD candidate UWAx1  
Francis Mitrou, BEc, PhD candidate, UWA

Dr Maryam Mozooni, (MD) PhD candidate, UWA  
Afrooz Najafzadeh, PhD candidate, UWA  
Barbara Nattabi, PhD candidate, Curtin  
Anett Nyaradi, MBBS MPH, PhD candidate, UWA  
Priya Parmar MSc, PhD Candidate  
Jan Payne SRN (UKCC), Post Grad Dip (Health  
Admin), MSc (Public Health), PhD  
Glenn Pearson, BA(Education), PhD candidate,  
UWA  
Bianca Petterson, (Doctorate of Pyschology)  
DPsych  
Marie Rye BSc (Hons), PhD Candidate  
Carrington Shepherd, PhD candidate, Curtin  
Dr Desiree Silva, MBBS, FRACP, MPH, PhD  
candidate, UWA  
Jessica Simons, PhD candidate, UWA  
Lydia Sung, PhD candidate, UWA  
Dr Alex Tan MBBS Masters Candidate  
Lauren Taylor, PhD candidate, UWA  
Jessica Tearne, PhD candidate, UWA  
Lisa Unwin, PhD candidate, UWA  
Anna Urbanowicz, BSc(OT)(Hons), PhD candidate  
ECU  
Stephanie Wade, PhD candidate, UWA  
Nicole Warrington BSc (Hons), PhD Candidate  
Elisha White MHlSci BSc BA CRFS, PhD  
Candidate  
Dr Scott White MBBS, PhD Candidate  
Sian Williams, PhD candidate, UWA

Janice Wong, BSc (Psych) (Hons), PhD candidate,  
UWA  
Kingsley Wong, MBBS MBA MSc AFCHSM, MPH  
candidate, UWA  
Paula Wyndow, BSc Postgraduate Diploma, PhD  
candidate, Curtin  
Seyan Yazar BMedSci MOrth, PhD Candidate

### THESES PASSED

Jaimi Andrews BSc (OT) (Hons) Edith Cowan  
University, Community participation for girls and  
women living with Rett syndrome.  
Kirsten Hancock, MSc Thesis, Swinburne  
University of Technology, "A longitudinal  
analysis of the association between maternal  
overprotection and children's physical health."  
Dr Sandra Louise BSc (Hons) PhD, University  
of Western Australia, Cardiovascular disease  
and depression: an investigation of common  
genes influencing early-life precursors and  
developmental trajectories for both conditions  
Elaine Tay, Doctorate of Clinical Psychology,  
The University of Western Australia, "Therapist  
Adherence in the Strong Without Anorexia  
Nervosa (SWAN) Study: Scale Development,  
Psychometrics, and a Preliminary Investigation  
of Therapist Adherence Data". Supervised by Sue  
Byrne and Karina Allen

### AWARDS

Karina Allen, Tracey Goodall Early Career Award  
2012, Australian Association of Cognitive  
Behaviour Therapy.

Carol Bower, Consumer and Community  
Participation Award, Stanley F, Bower C, de Klerk  
N, Leonard H, Silburn S, Zubrick S, Payne J, Scott  
L. National Health and Medical Research Council  
2010-2014 Program Grant - Early Developmental  
Pathways linking health, disability, education,  
welfare and justice.

Jenny Downs. New Independent Researcher  
Infrastructure Award, WA Health Department,  
June 2012

Jenny Fairthorne. Australian Society for  
Intellectual Disability (ASID) WA, Student Travel  
Award, 2012

Stephanie Fehr. Stan & Jean Perron Scholarship,  
2012

Kitty Foley. Stan Perron Award for Excellence,  
2012

Deborah Lehmann, Officer (AO) in the  
General Division of the Order of Australia. For  
distinguished service to medical research in the  
field of epidemiology, particularly the prevention  
of pneumococcal infection, to Indigenous health,  
and to professional organisations. June 2012.

Hannah Moore, Aileen Plant Memorial Prize in  
Infectious Disease Epidemiology – Finalist

Wendy Oddy, TICHR Scientist Leadership Award,  
Registered Public Health Nutritionist (RPHNutr).

Melissa O'Donnell, 2012 PhD Supervisor of the  
Year

Jan Payne, Consumer and Community  
Participation Award, Stanley F, Bower C, de Klerk  
N, Leonard H, Silburn S, Zubrick S, Payne J, Scott  
L. National Health and Medical Research Council  
2010-2014 Program Grant - Early Developmental  
Pathways linking health, disability, education,

welfare and justice.

Monique Robinson, Scopus Elsevier Outstanding Performance Star Award 2012.

Anna Urbanowicz. The Friends of the Institute for Child Health Research Travel Grant, 2012; Stan & Jean Perron Scholarship, 2012; Edith Cowan University Three Minute Thesis Competition 2012 Runner-up

## External Committees

### INTERNATIONAL

Carol Bower. International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Nominating Committee

Carol Bower. Faculty member, Training Program in Birth Defects Surveillance, run jointly by WHO, CDC and ICBDSR

Kitty Foley, Student Representative, IAASSID International Family Special Interest Research Group, 2012-

Deborah Lehmann. Papua New Guinea Institute of Medical Research Buttressing Coalition member (1998-).

Helen Leonard, Member of Autism Speaks International Autism Epidemiology Network Workgroup, (2007-).

Helen Leonard, Member of Executive of RettSearch, International Consortium of Rett Syndrome Clinical Researchers (2009-).

Wendy H. Oddy. International Consultative and Advisory committee, Early Nutrition.

Wendy H. Oddy. Recommendations Development Panel, Early Nutrition Project,

Munich, Germany.

Melissa O'Donnell. International Society for the Prevention of Child Abuse and Neglect (2007-present)

Melissa O'Donnell. International Child Maltreatment Data Working Group (2009-present)

Monique Robinson, Scientific Committee Member for the 7th World Conference on the Promotion of Mental Health and the Prevention of Mental and Behavioural Disorders, Perth Australia (2012).

Catherine L. Taylor. Member of the New Zealand Health Research Council, Assessing Committee (2012).

### NATIONAL

Carol Bower, National Perinatal Statistics Unit Steering Committee for Congenital Anomalies

Carol Bower, Australian Paediatric Surveillance Unit Scientific Review Panel

Carol Bower, Australian Paediatric Surveillance Unit Board Chair

Carol Bower, National Perinatal Epidemiology and Statistics Unit Fetal Alcohol Spectrum Disorder

Sally Brinkman, Vice President of the Board, Playgroups Association of South Australia.

Brad Farrant, Australian Research Alliance for Children and Youth's representative on the Climate and Health Alliance's committee of management (2012)

Tanyana Jackiewicz, National Child and

Community Health Council (2007)

Heather Jones. Australasian FASD Conference 19-20 November 2013, Conference Organising Committee and Stakeholder Advisory Group

Deborah Lehmann. Data safety monitoring board of the PneuMum Maternal pneumococcal immunisation study in Northern Territory (2005-2012)

Deborah Lehmann. Data safety monitoring board of CHIRRP "Combating H. *influenzae* related respiratory pathology" (2012-)

Deborah Lehmann. Member of Conference Committee for the 19th International Symposium on Recent Advances in Otitis Media (RAOM) (2012)

Deborah Lehmann. Participant in the Standing Committee on Health and Ageing Roundtable - Health issues across international borders (2012)

Helen Leonard, Member of Executive, Australian Association of Developmental Disability Medicine, (2002-).

Raewyn Mutch. Australasian FASD Conference 19-20 November 2013, Stakeholder Advisory Group

Wendy Oddy, Preventive and Community Health Committee, NHMRC.

Wendy Oddy, Assistant Chair, Grant review panel, NHMRC.

Catherine L Taylor, Sustained Nurse Home Visiting (INHV) Project (ARACY and the Centre for Community Child Health), Member of the Expert Reference Group.

Catherine L Taylor, ARACY State Convenor (WA)

Catherine L Taylor, Australian Research Alliance for Children and Youth (ARACY), Councillor.

Catherine L Taylor, New Investigators Network, Australian Research Alliance for Children and Youth (ARACY), Mentor.

Catherine L Taylor, International Journal of Speech-Language Pathology, Member of the Executive Board.

Catherine L. Taylor, Member, Expert Reference Group Economic Modeling. Department of Education and Child Development, Adelaide, South Australia.

Catherine L. Taylor, Member, Executive Project Group for the Fraser Mustard Centre, Department for Education and Child Development, Government of South Australia.

Rochelle Watkins, Member, Board, The National Organisation for Fetal Alcohol Syndrome and Related Disorders

### LOCAL

Jenny Bourke, Director, Board of Management, Parents of Children with Disabilities (Inc), Kalparrin.

Jenny Bourke, Member of Scientific Advisory Council, SIDS and Kids WA

Carol Bower, Perinatal and Infant Mortality Committee Department of Health WA

Carol Bower, Prenatal Diagnosis Committee, Department of Health WA

Carol Bower, Alcohol Advertising Review Board, Panel Member

Carol Bower, WA Department of Health,

Child and Youth Network Fetal Alcohol Spectrum Disorder Model of Care. Secondary Implementation Working Group; Co-lead

Jenny Downs. Human Research Ethics Committee, Princess Margaret Hospital for Children (2010 - ).

Jenny Downs. Committee Member, Consumer and Community Advisory Council, Telethon Institute for Child Health Research (2012 - ).

Rebecca Glauert. Ngala Professional Advisory Committee (2011 – present)

Rebecca Glauert. Data Linkage Advisory Board (2010 – present)

Tanyana Jackiewicz, Commissioner for Children and Young People Expert Reference Group: Wellbeing Indicators Group, (2009-)

Tanyana Jackiewicz, Child and Youth Health Network, Executive Advisory Group, (2006-)

Heather Jones, Focus on FASD in WA Forum February 2012. Organising Committee

Heather Jones, WA Department of Health, Child and Youth Network Fetal Alcohol Spectrum Disorder Model of Care. Member of Tertiary Implementation Working Group

Heather Jones, Injury Control Council of WA, Community Safety Programs

David Lawrence, Heathway Research Committee, (2010-)

Deborah Lehmann. Perinatal and Infant Mortality Committee, Ministry for Health, WA, Deputy to Carol Bower (2005-)

Deborah Lehmann. Meningitis Centre Management Committee (1998-).

Deborah Lehmann. Testimony as an expert in otitis media in Aboriginal and non-Aboriginal children to the Parliament of Western Australia Education and Health Standing Committee Aug 23 2012.

Helen Leonard, Women's and Newborns' Health Network Executive Advisory Group.

Helen Leonard, Executive Committee Perth Epidemiology Group, (2008-).

Miriam Maclean. Perinatal Mental Health Services Research Committee (July 2010 – present)

Miriam Maclean. Marce Society Conference Local Organising Committee (January 2011 – present)

Hannah Moore. Meningitis Centre Management Committee.

Jan Payne. WA Department of Health, Child and Youth Network Fetal Alcohol Spectrum Disorder Model of Care. Member of Primary Prevention Implementation Working Group

Jan Payne. Alcohol Advertising Review Board, Panel Member

Glenn Pearson. Health Consumer Council of Western Australia

Glenn Pearson. Curtin University Human Research Ethics Committee

Glenn Pearson. Telethon Institute for Child Health Research Consumer and Community Advisory Council

Glenn Pearson – Key Aboriginal Advisory Group, Strong Spirit Strong Future - Promoting Healthy Women and Pregnancies 2011

Glenn Pearson – Meningitis Centre Committee 2012

Desiree Silva. Head of Department Medical Advisory Committee (HOD/MAC) Joondalup Health Campus

Desiree Silva- Chair of the Royal Australasian College of Physicians

Desiree Silva- State Paediatric Implementation Plan

Anna Urbanowicz, Research and Development Committee Member, WA Occupational Therapy Association (2012 -).

Rochelle Watkins. Member, Board of Directors, Neurological Council of Western Australia

Amanda Wilkins. WA Department of Health, Child and Youth Network Fetal Alcohol Spectrum Disorder Model of Care. Member of Tertiary Implementation Working Group

Janice Wong. The Australian Association of Cognitive Behavioural Therapy (December 2010)

## Invited Presentations

### INTERNATIONAL

Alison Anderson. Celebrating 10 years: Achievements of the InterRett project, 7<sup>th</sup> World Rett Syndrome Congress, Translational and Pre-Clinical Research Symposium, June 22-24 2012, New Orleans, USA (poster).

Eve Blair. The role of smoking in pregnancy in the aetiology of cerebral palsy in term and late preterm singletons: analysis of CCCP data. 4<sup>th</sup> International CP Conference, Pisa, Italy, October 2012.

Eve Blair. The role of pregnancy-induced hypertension in the aetiology of cerebral palsy in term and late preterm singletons: analysis of CCCP data. 4<sup>th</sup> International CP Conference, Pisa Italy, October 2012.

Eve Blair. Issues in estimating prevalence and trends in cerebral palsy. Keynote lecture, 4<sup>th</sup> International CP Conference, Pisa Italy, October 2012.

Eve Blair. A new analytical approach to further understand the aetiology of CP: analysis of CCCP data. 4<sup>th</sup> International CP Conference, Pisa Italy, October 2012.

Eve Blair. Beginning to unravel the causal pathways to CP for low risk term infants: analysis of CCCP data. 4<sup>th</sup> International CP Conference, Pisa Italy, October 2012.

Eve Blair. Reliable description of motor impairments in children with CP. 4<sup>th</sup> International CP Conference, Pisa Italy, October 2012.

Eve Blair. Achieving mandatory notification of cerebral palsy in Western Australia – a success story. 4<sup>th</sup> International CP Conference, Pisa Italy, October 2012.

Eve Blair. Fetal growth and perinatal and paediatric outcomes. Plenary presentation, First International Conference on Fetal Growth, Birmingham UK, September 2012.

Eve Blair. Analysing MOBAND (MOTHERS and BABIES of Norway and Denmark). Invited lecture concerning the analysis of MOBAND data relevant to cerebral palsy. Bergen, Norway, May 2012.

Eve Blair. Acute intrapartum hypoxic events



and cerebral palsy: Is this a complete pathway? *American Academy of Cerebral Palsy and Developmental Medicine*, Toronto, Canada, 2012. (This paper is a finalist for best paper of American Academy.)

Sally Brinkman. The challenges of cultural validity in early child development measures. Invited Keynote. University of British Columbia Faculty Retreat. Vancouver, Canada. March.

Brinkman S. Engelhardt D. (2012). The status of data linkage in Australia. Invited Presentation. Manitoba Centre for Health Policy. Winnipeg, Canada. March.

Sally Brinkman. Australia's Experience with the Early Development Instrument. Invited Keynote Presentation. Department of Education and Communities. Children's Conference. Dublin, Ireland, April.

Sally Brinkman. Midline Findings – RCT evaluating the impact of the community based early childhood education and child development program across Indonesia. Invited Presentation. World Bank. Jakarta, Indonesia. June.

Jenny Downs. Epilepsy in MECP2 mutated Rett syndrome using international data, 7<sup>th</sup> World Rett Syndrome Congress, Translational and Pre-Clinical Research Symposium, June 22-24 2012, New Orleans, USA (poster).

Jenny Downs. Physical activity and Rett syndrome, 7<sup>th</sup> World Rett Syndrome Congress, Translational and Pre-Clinical Research Symposium, June 22-24 2012, New Orleans, USA.

Jenny Downs. Scoliosis and orthopaedic issues, 7<sup>th</sup> World Rett Syndrome Congress, Family

Education and Awareness Sessions - Workshop, June 22-24 2012, New Orleans, USA.

Stephanie Fehr. Rational and processes in the development of a CDKL5 disorder database. International CDKL5 Research Symposium. 27<sup>th</sup> June 2012, New Orleans, USA.

Stephanie Fehr. The CDKL5 disorder: a new cause of early-onset encephalopathy. 7<sup>th</sup> World Rett Syndrome Congress. 22<sup>nd</sup>-26<sup>th</sup> June 2012, New Orleans, USA.

Stephanie Fehr. The New CDKL5 disorder database. 7<sup>th</sup> World Rett Syndrome Congress. 22<sup>nd</sup> – 26<sup>th</sup> June 2012, New Orleans, USA.

Kitty Foley. Behaviour changes over seven years for young adults with Down syndrome transitioning from school to post school. International Association for the Scientific Study of Intellectual and Developmental Disabilities, July, 2012 Halifax, Nova Scotia

Kitty Foley. Family quality of life of young adults transitioning from school to post-school for young adults with Down syndrome. International Association for the Scientific Study of Intellectual and Developmental Disabilities, July, 2012 Halifax, Nova Scotia

Kitty Foley. Family quality of life of young adults with Down syndrome transitioning from school to post-school. 47<sup>th</sup> Annual Conference for the Australasian Society for Intellectual Disability, Wellington, New Zealand, November, 2012

Kitty Foley. Functioning of young adults with Down syndrome transitioning into post school day occupations. International Association for the Scientific Study of Intellectual and Developmental Disabilities, July, 2012 Halifax, Nova Scotia

Noula Gibson. The CP Description Form. North of England Collaborative Cerebral Palsy Survey (NECCPS) meeting, Durham UK, February 2012.

Noula Gibson. The Australian Spasticity Assessment Scale (ASAS). Newcastle-Upon-Tyne Hospitals Trust, Newcastle Upon Tyne UK, February 2012.

Noula Gibson. How the Australian Spasticity Assessment Scale (ASAS) and the CP Description Form can be used in Brazilian sports classification systems. Keynote speaker, Cerebral Palsy International Sports & Recreation Association (CPISRA) Classification Committee Biennial Meeting, Rio de Janeiro, Brazil, November 2012.

Sonya Girdler. 'I have a good life': The meaning of well-being from the perspective of young adults with Down syndrome. 7<sup>th</sup> November 2012, ASID Conference, New Zealand, 2012.

Fiona Stanley, Rebecca Glauert & Sally Brinkman. A whole of Government Approach to Improving Child Wellbeing, OECD World Forum on Measuring Wellbeing, Delhi, India, October, 2012

Rebecca Glauert. "Linking Data to Build an Evidence Base", WA Department of Treasury, Perth WA, November 2012

Rebecca Glauert & Scott Sims. "The Developmental Pathways Project- On the path to Prevention" WA Crime Prevention Council, Perth WA, July 2012

Rebecca Glauert & Scott Sims. "Liquor Outlet Density Mapping" WA Crime Prevention Council, Perth, WA. November 2012

Rebecca Glauert & Melissa

O'Donnell. "Developmental Pathways Project: Joined up data and Joined up thinking- Data Linkage and Child Protection" Report on Government Services, Child Protection Working Group. July 2012, Perth, WA

Amanda Langridge. International Collaboration of Autism Registry Epidemiology (iCARE) In-person Meeting. Turku, Finland, February 2012.

Helen Leonard. Databases: the importance of family and patient contributions to our collective understanding of Rett syndrome. World Rett Syndrome Congress 2012, New Orleans, June 2012.

Helen Leonard. Why we need population-based and longitudinal study designs: the example of the Australian Rett Syndrome Study, 7<sup>th</sup> World Rett Syndrome Congress, Translational and Pre-Clinical Research Symposium, June 22-24 2012, New Orleans, USA (poster).

Wendy Oddy. Early Nutrition Workshop, Obergurgl, Austria and Munich, Germany.

Wendy Oddy. The 1<sup>st</sup> International Nutrition and Growth conference, Paris, France, March.

Wendy Oddy. Society for Longitudinal and Life Course Studies, Paris, October.

Terri Pikora. Accommodation needs for young people with Down Syndrome in WA – Parents' Perspective. 47<sup>th</sup> Annual Australasian Society for Intellectual Disability Conference, New Zealand, November, 2012

Carrington Shepherd. 3-Generation Data on Aboriginal People in Australia, 102<sup>nd</sup> Annual Meeting of the American Psychopathological Association, 1-3 March 2012, New York, USA.

Desiree Silva- "Early Risk Factors and Education

and Justice Outcomes of Children Diagnosed and treated for ADHD in WA: A Population Linkage Study". First Asian Congress on ADHD, Seoul, November 2012

Catherine L. Taylor. Member of the New Zealand Health Research Council, Assessing Committee, 2012.

Anna Urbanowicz. A longitudinal analysis of communication abilities in girls and women with Rett syndrome. 7<sup>th</sup> World Congress on Rett syndrome, New Orleans, Louisiana, June 2012 (*poster*).

Anna Urbanowicz. A qualitative understanding of factors influencing communication in Rett syndrome. 7<sup>th</sup> World Congress on Rett syndrome, New Orleans, Louisiana, June 2012 (*poster*).

## NATIONAL

Karina Allen, "The onset and persistence of eating disorder symptoms: What places children and adolescents at risk and how can we promote resilience?" Invited keynote address at the 35<sup>th</sup> National Conference of the Australian Association of Cognitive Behaviour Therapy, Gold Coast, October 2012.

Alison Anderson The international Rett syndrome database InterRett: an exemplary model for rare disease research, 12<sup>th</sup> International Child Neurology Conference, Brisbane, QLD, June 2012.

Eve Blair. Developing confidence in interpreting the results of research. Workshop, AusACPDM Biennial Conference, Brisbane, June 2012.

Katherine Bathgate. The "Ins and Outs" of meal-times for people with Rett syndrome. Australian

Rett Syndrome Family Conference, Brisbane, May 26 2012.

Ami Bebbington. Investigating hospital morbidity in individuals with Intellectual Disability and/or Autism spectrum disorders using the Western Australian Data Linkage System. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, March 2012.

Ami Bebbington. Survival with Rett syndrome: comparing Rett's original sample with data from the Australian Rett Syndrome Database. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, NSW, March 2012.

Eve Blair. Cerebral palsy in term and late preterm born singletons and macroscopically identified placental infarction (winner of CP Alliance Best Paper in Prevention and Cure category). AusACPDM/ICNA Conference, Brisbane, May 2012.

Eve Blair. Systematic review of risk factors for term infants. *Perinatal Society of Australia and New Zealand*, Sydney, 2012.

Eve Blair. Acute intrapartum hypoxic events and cerebral palsy: Is this a complete pathway? Perinatal Society of Australia and New Zealand, Sydney, 2012.

Eve Blair. Systematic review of risk factors for term infants. Australasian Academy of Cerebral Palsy and Developmental Medicine, Brisbane, 2012.

Carol Bower. Alcohol and Pregnancy. Out of sight; out of mind Foundation for Alcohol Research and Education, Melbourne.

Brinkman S. How well are we raising our Children? Invited Keynote Presentation. Freeling Community Forum. Freeling, Australia. March.

Sally Brinkman. How do children in South Australia compare to their counterparts interstate and internationally. Invited Keynote. MS McLeod Research Seminar. Women's and Children's Health Network. Adelaide, Australia, April.

Sally Brinkman. Understanding the AEDI Results and Implications for my Community. AEDI Community Forum. Invited Keynote Presentation. Campbelltown City Council, February.

Sally Brinkman. Child and Parent Centres: An Update for the Community Sector. Social Policy Forum. Invited Keynote. Western Australian Council of Social Services (WACOSS). Perth, Australia, November.

Sally Brinkman. What does the AEDI tell me about children across the Eyre Peninsula? Our Children Our Future Regional Conference. Invited Keynote. Port Lincoln, Australia, May.

Sally Brinkman. Use of Population Data for Local Level Planning. Invited Presentations for Professional Development Training. Children's Centres Leaders Day. Glenelg, Australia. June.

Sally Brinkman. Implications of the AEDI data for South Australian Children. Invited Presentation to the South Australian Every Chance for Every Child Cabinet Taskforce. Adelaide, Australia, June.

Sally Brinkman., Pradhan M, Hasan A, Kinnell A, Jung H. (2012) Early Childhood Education and Development in Indonesia: findings from on-going impact evaluation. Invited Policy Audience

Presentation. AusAID, Canberra, Australia. August.

Sally Brinkman. Translational Science Fostering Integration. The National Early Years Symposium. Invited Presentation. Adelaide, Australia, September.

Sally Brinkman. The Australian Early Development Index (AEDI): a tool for planning, policy and evaluation. Invited Keynote. NATSEM Workshop Series. Canberra, Australia, September.

Sally Brinkman. What does AEDI & Census Data tell us about our region? Invited Presentation. Getting Connected in the Urban Village ~ Southern Adelaide Conference. Morphettville, Australia, September.

Sally Brinkman. Liberating Data through Data Linkage. Invited Presentation. ACT Director Generals Monthly Social Policy Meeting. Canberra, Australia, October.

Jenny Downs. Determinants of functional abilities in Rett syndrome, 12<sup>th</sup> International Child Neurology Conference, Brisbane, Australia. May 28-June 1, 2012.

Jenny Downs. How does genotype influence the early clinical presentation in Rett syndrome? 12<sup>th</sup> International Child Neurology Conference, Brisbane, Australia. May 28-June 1, 2012.

Jenny Downs. Longitudinal research throughout life: The need for international collaboration, IN Special Interest Group, Health and outcomes in children and young adults with neurological and developmental conditions, 12<sup>th</sup> international Child Neurology Conference, Brisbane, Australia. May 28-June 1, 2012.

Jenny Downs. Mobility, recreation and bone health. Australian Rett Syndrome Family Conference, Brisbane, Australia. May 25-26, 2012.

Jenny Downs. Scoliosis. Australian Rett Syndrome Family Conference, Brisbane, Australia. May 25-26, 2012.

Jenny Downs. Variable presentations of Rett syndrome. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, Australia. March 8-10, 2012.

Jenny Fairthorne. The physical, mental and overall health of the parents of children with intellectual disability compared to that of parents of children without disabilities: a review. 47<sup>th</sup> Annual Australasian Society for Intellectual Disability Conference, November, 2012.

Stephanie Fehr. The CDKL5 disorder: a new cause of early-onset encephalopathy. Australia Association of Developmental Disability Medicine. 8<sup>th</sup> – 10<sup>th</sup> March, 2012, Sydney.

Stephanie Fehr. 12<sup>th</sup> The CDKL5 disorder: a new cause of early-onset encephalopathy. International Child Neurology Congress and 11<sup>th</sup> Asian and Oceanian Congress of Child Neurology. 27<sup>th</sup> May – 1<sup>st</sup> June, 2012, Brisbane.

Patrick Fitzgerald. Patterns of hospitalisation in Down syndrome children born in Western Australia. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, NSW, March 2012.

Kitty Foley. Impact Of Health On Post-School Day Occupations For Young People With Down Syndrome. Australian Association of Developmental Disability Medicine (AADDM)

2012 Conference, Sydney, NSW, March 2012.

Kitty Foley. Transitioning Young Adults with Down Syndrome: A longitudinal analysis. Disability Employment Australia Conference, Melbourne, Vic. August, 2012

Geoffrey Hammond. Is there a relationship between seasonality, month of birth and autism?: results from the iCARE study. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, NSW, March 2012 (poster).

Heather Jones. Country Magistrates Conference, November 2012

Amanda Langridge. Maternal Conditions And Perinatal Characteristics Associated With Autism Spectrum Disorder And Intellectual Disability. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, NSW, March 2012.

David Lawrence & Francis Mitrou. Managing confidentiality in data linkage workshop, Data linkage and integration: Bringing data together to support decision making, June 2012, Canberra.

Helen Leonard. Advances in Research and Therapy in Autism Spectrum Disorders and Related Conditions. Symposium. Advances in Rett Syndrome Clinical Research International Child Neurology Congress 2012, Brisbane, May 2012.

Helen Leonard. Data Linkage: A powerful tool for population-based intellectual disability research. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, NSW, March 2012

Helen Leonard. Psychosocial and economic impacts of Rett syndrome on families. APSU Rare Diseases Workshop Sydney, March 2012.

Helen Leonard. Rett syndrome: From research to clinical guidelines. APSU Rare Diseases Workshop, Sydney, March 2012.

Helen Leonard. Trends in intellectual disability in Western Australia. Australian Association of Developmental Disability Medicine (AADDM) 2012 Conference, Sydney, NSW, March 2012.

Helen Leonard. Update on Rett Syndrome Clinical Research. Rett Syndrome Family Conference 2012, Brisbane, May 2012.

Francis Mitrou. Fragile Families Workshop, University of Queensland, 23-24 July 2012, Brisbane.

Raewyn Mutch. FASD Training and Seminars: Health Ed/ Generation Next, RACGP Accredited, Brisbane, Queensland

Raewyn Mutch. 2<sup>nd</sup> Tasmanian FASD Conference, March 2012

Raewyn Mutch. Focus on FASD Forum, March 2012. Knowledge, attitudes and practice within justice across Western Australia.

Raewyn Mutch. Child and Adolescent Health Research Symposium October 2012. Professional knowledge attitudes and practice of FASD in the WA criminal justice system.

Raewyn Mutch. Child and Adolescent Health Research Symposium, October 2012. No fear asking about alcohol use in pregnancy: closing a gap in care and considering Fetal Alcohol Spectrum Disorders.

Wendy Oddy. Educational seminar, Nestlé, Perth

WA.

Catherine Taylor. Clinical assessment of finiteness marking in children's language acquisition: Keynote Workshop presented at the Speech Pathology Australia National Conference, Hobart, Tasmania, June, 2012.

Catherine Taylor. A study of growth in receptive vocabulary 4-8 years projected to literacy at 10 years. Paper presented at the Early Years Seminar, Murdoch Children's Research Institute, Melbourne, Victoria, April, 2012.

Anna Urbanowicz. An analysis of communication abilities in girls and women with Rett syndrome. 12<sup>th</sup> International Child Neurology Congress, Brisbane, Queensland, Brisbane, May 2012.

Anna Urbanowicz. Communication. Australian Rett Syndrome Family Conference, Brisbane, May 2012.

Rochelle Watkins, Focus on FASD Forum, March 2012. Development of a diagnostic instrument for fetal alcohol spectrum disorders in Australia: project update.

Rochelle Watkins, Child and Adolescent Health Research Symposium, October 2012. Health professionals' perceptions about the adoption of existing diagnostic guidelines for fetal alcohol spectrum disorders in Australia.

Amanda Wilkins, Focus on FASD Forum, March 2012 Evaluation of FASD information and services for foster carers.

## LOCAL

Katherine Bathgate. Parent perceptions of overweight and obesity in young adults with

Down syndrome. The Australasian Society for Intellectual Disability, WA State Conference, September 7, 2012, Perth.

Eve Blair. Developing confidence in interpreting the result of research. PMH Grand Round, Perth, October 2012.

Eve Blair. Causation of CP including prevention strategies: contemporary views. Invited lecture to Graduate Diploma of Neurological Rehabilitation (Paediatrics), The Centre for Musculoskeletal studies, UWA, Perth, July 2012.

Eve Blair. Interpreting the results of research. Invited lecture to Graduate Diploma of Neurological Rehabilitation (Paediatrics), The Centre for Musculoskeletal studies, UWA, Perth, July 2012.

Eve Blair. Causal pathways to CP. Invited presentation, International Child Neurology Association Mini-Satellite Meeting, PMH, Perth, June 2012.

Jenny Bourke. Patterns of hospitalisations for children with intellectual disability and/or autism. Australian Society for Intellectual Disability (WA) 2012 Conference, Perth WA, September 2012

Jenny Bourke . Trends in prevalence of intellectual disability in WA. International Data Linkage Conference 2012, Perth, Australia, May 2012 (*poster*).

Daniel Christensen, David Lawrence, Francis Mitrou. Getting Our Story Right: A cross agency data linkage and analysis project to better understand and improve information about Aboriginal and Torres Strait Islander peoples using administrative data collections. TICH Child Health Research Seminar, 30 March 2012,

Perth.

Jenny Downs. Back posture in boys and young men with Duchenne Muscular Dystrophy in Nepal, MD2012 Symposium, World Muscle Society, October 8 2012, University of Western Australia, Perth, Australia

Jenny Downs. Objective measurement of natural living physical activity in Rett syndrome forms the basis of advocacy, The Australasian Society for Intellectual Disability, WA State Conference, September 7, 2012, Perth.

Jenny Downs. Updated physiotherapy approach to rare conditions: A focus on Rett syndrome, for Graduate Diploma of Neurological Rehabilitation (Paediatrics), August 8 2012, University of Western Australia, Perth.

Kristjana Einarsdottir. Birth outcomes by mode of delivery in Western Australian public and private patients. International Data Linkage Conference 2012, Perth, Australia, May 2012.

Jenny Fairthorne. A priori differences of mothers of children with intellectual disability and/or autism spectrum disorder: a systematic review of the literature. Australian Society for Medical Research, WA (ASMRWA), Edith Cowan University, Perth, WA, 7<sup>th</sup> June, 2012.

Stephanie Fehr. The CDKL5 Disorder. Neuroepidemiology Research Group Meeting. 13<sup>th</sup> June, Perth, W.A.

Stephanie Fehr. The CDKL5 Disorder: a new cause of early-onset encephalopathy. Telethon Institute for Child Health Research Seminar Series. 2<sup>nd</sup> March, 2012, Perth, W.A.

Brad Farrant. Climate change, child health and development, Telethon Institute for Child Health

Research, Perth.

Kitty Foley. Psychopathology of adolescents with Down syndrome: Changes over time and post-school day occupations. Child and Adolescent Health Research Symposium, PMH, WA, October, 2012

Geoffrey Hammond. The relationship between trends in caesarean delivery at preterm gestation and neonatal mortality in Western Australia. International Data Linkage Conference 2012, Perth, Australia, May 2012.

Geoffrey Hammond. The use of harmonized, population representative multinational data to assess the relationship between seasonality, month of birth and autism: results from the iCARE study. International Data Linkage Conference 2012, Perth, Australia, May 2012 (*poster*).

Amanda Langridge. Maternal conditions and perinatal characteristics associated with Autism Spectrum Disorder and intellectual disability. International Data Linkage Conference 2012, Perth, May 2012.

Amanda Langridge. Mode of delivery and autism spectrum disorders-is there an association? International Data Linkage Conference 2012, Perth, Australia, May 2012 (*poster*).

David Lawrence. Presentation on the Second Child and Adolescent Component of the National Survey of Mental Health and Wellbeing, Mental Health Commission, 26 November 2012, Perth.

David Lawrence & Kate Hafekost. Practical approaches to analysis of linked data: protecting confidentiality, WA Department of Health, 31 August 2012, East Perth.

Deborah Lehmann. The Kalgoorlie Otitis Media Research Project: Epidemiology of upper respiratory tract carriage in Aboriginal and non-Aboriginal children and associations between carriage and disease and mucosal immunity. Combined Biological Sciences Meeting of the Australian Society for Microbiology Perth WA, Aug 24 2012.

Raewyn Mutch. Princess Margaret Hospital Child and Adolescent Health Research Symposium, October 2012.

Developing an adjunct service for considering Fetal Alcohol Spectrum Disorders (FASD); applying the University of Washington (UW) 4-Digit- FASD Facial Photographic Analysis through the department of Medical Illustrations

Jan Payne. Fetal Alcohol Spectrum Disorder. Ngaangk-Moort Women's Group. Brookman House Child and Family Centre. Langford. Invited presentation. March 2012.

Monique Robinson. Stress in pregnancy: Is our research causing it? Telethon Institute for Child Health Research, Perth.

Monique Robinson. Early life origins of behaviour, Department of Health & National Perinatal Depression Initiative, 21 February 2012, Graylands Hospital.

Monique Robinson. Early life origins of behaviour, Department of Health Clinical Practice Update, 21 March 2012, East Perth.

Carrington Shepherd. Closing the Gap in mental health outcomes: Do socioeconomic conditions matter? Telethon Institute for Child Health Research: Child Health Research Seminar Series, 11 May 2012, Perth.

Kingsley Wong. Influences of age and MECP2 genotype on epilepsy in Rett syndrome. Child and Adolescent Health Research Symposium, Perth, Australia, Oct 2012.

## Active collaborations

### AEDI

Matthew Hardy and Robyn Priddle, Department of Education, Employment and Workplace Relations, Canberra, Australia

David Engelhardt, Department for Education and Child Development, South Australia, Australia

Sharon Goldfeld, Royal Children's Hospital Centre for Community Child Health, Melbourne, Australia

Dr Amer Hasan, World Bank Indonesia, Jakarta, Indonesia

Professor Menno Pradhan, VU University, Amsterdam, The Netherlands

Professor John Lynch, The University of Adelaide, Australia

Associate Professor Magdalena Janus, McMaster University, Hamilton, Canada

Associate Professor Kimberley Schonert-Reichl and Dr Martin Guhn, University of British Columbia, Vancouver, Canada

### BIRTH DEFECTS

Carol Bower

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower and Professor Elizabeth Elliott AM, Steering

group of health professionals, researchers, epidemiologists and consumers and community members

Rochelle Watkins

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower and Professor Elizabeth Elliott AM, Steering group of health professionals, researchers, epidemiologists and consumers and community members

Jan Payne

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower and Professor Elizabeth Elliott AM, Steering group of health professionals, researchers, epidemiologists and consumers and community members

Injury Control Council of WA, Sarai Stevely, Community Safety Programs

Raewyn Mutch

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower and Professor Elizabeth Elliott AM, Steering group of health professionals, researchers, epidemiologists and consumers and community members

Amanda Wilkins

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower

and Professor Elizabeth Elliott AM, Steering group of health professionals, researchers, epidemiologists and consumers and community members

Heather Jones

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower and Professor Elizabeth Elliott AM, Steering group of health professionals, researchers, epidemiologists and consumers and community members

## CHILDHOOD CANCER INTERNATIONAL

Patricia Buffler, University of California, Berkeley USA

Catherine Mettayer, University of California, Berkeley USA

Jacqueline Clavel Inserm, CESP Centre for research in Epidemiology and Population Health, U1018, Environmental epidemiology of cancer Team, F-94807, Villejuif, France; Univ Paris-Sud, UMRS 1018, F-94807, Villejuif, France

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## AUSTRALIA

Michael Fenech, CSIRO Nutrigenomics, Adelaide.

Bruce Armstrong, Sydney School of Public Health, University of Sydney, NSW

Frank van Bockxmeer, Royal Perth Hospital, WA

Michelle Haber, Children's Cancer Institute Australia, NSW

Rodney Scott, Hunter Medical Research Institute, University of Newcastle, NSW and Hunter Area Pathology Service, NSW

John Attia, Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, NSW, Department of Medicine, John Hunter Hospital and Hunter Medical Research Institute, NSW.

Murray Norris, Children's Cancer Institute Australia, NSW

Lin Fritschi, WA Institute for Medical Research, University of Western Australia, WA

Margaret Miller, Edith Cowan University, WA  
 Judith Thompson, WA Cancer Registry, WA  
 Frank Alvaro, John Hunter Hospital, Newcastle, NSW  
 Catherine Cole, Princess Margaret Hospital for Children, WA  
 Luciano *Dalla Pozza*, *Children's Hospital at Westmead, NSW*  
 John Daubenton, Royal Hobart Hospital, Tasmania  
 Peter Downie, Monash Medical Centre, Melbourne, Victoria  
 Liane Lockwood, Royal Children's Hospital, Brisbane, Queensland  
 Maria Kirby, Women's and Children's Hospital, Adelaide, SA  
 Glenn Marshall, Sydney Children's Hospital, Sydney, NSW  
 Elizabeth Smibert, Royal Children's Hospital, Melbourne, Victoria  
 Ram Suppiah, Mater Children's Hospital, Brisbane, Queensland

**COLLABORATION FOR APPLIED RESEARCH AND EVALUATION (CARE)**

Dr Brad Jongeling, Paediatrician, Child Development Service, Community and Child Health, Child and Adolescent Health Service  
 Craig Russell, Specialist Clinical Psychologist, Child Adolescent Mental Health Service, Child and Adolescent Health Service  
 Sue Kiely, Senior Coordinator Workforce Development, Community and Child Health,

Child and Adolescent Health Service  
 Anne-Marie McHugh, State wide coordinator, Aboriginal Maternity Service Support Unit (AMSSU), Women and Newborn Health Service / Aboriginal Health Council of Western Australia  
 Angela O'Connor and Renate McLaurin, Drug and Alcohol Midwives, Women and Newborns Drug and Alcohol Service, Women and Newborns Health Service  
 Terri Barrett, Director Midwifery, King Edward Memorial Hospital, Womens and Newborns Health Service  
 Professor Yvonne Hauck, Professor of Midwifery, Curtin University, King Edward Memorial Hospital, Women and Newborns Health Service  
 Anne Rae, Director Allied Health and Head: Nutrition and Dietetics, King Edward Memorial Hospital, Women and Newborns Health Service  
 Dr Janet Hornbuckle, Co-Lead, Women and Newborns Health Network  
 Graeme Boardley, Co-Lead, Women and Newborns Health Network  
 Professor Karen Edmund, Winthrop Professor, Aboriginal Clinical Child Health and Consultant Paediatrician, Child and Adolescent Health Service  
 Kerryl Spence and Karen Oglivie, Midwives, Kaleeya Hospital, South Metropolitan Area Health Service  
 Keren Geddes, Specialist Clinical Psychologist, Child Adolescent Mental Health Service Rockingham, Child and Adolescent Health Service  
 Sue Bradshaw, Principal Policy Officer,

Community and Child Health, Child and Adolescent Health Service  
 Michelle Gray, Principal Policy Officer, Western Australian Drug and Alcohol Authority  
 Dr Darryl Efron, Paediatric Research Network, Murdoch Childrens Research Institute  
 Dr Emma Sciberras, Post Doctoral Research Fellow, Community Child Health, Population Health, Genes and Environment  
 Associate Professor Harriet Hiscock, Paediatrician, Centre for Community Child Health, The Royal Children's Hospital Leader, Healthcare Innovation Affinity Group, Murdoch Childrens Research Institute, Principal Fellow, Department of Paediatrics, The University of Melbourne  
 Dr Angela Luangrath, Senior Fellow, Centre for Community Child Health, Royal Children's Hospital  
 Professor Ric Fordham, Economist, East Anglia University  
 Emeritus Professor Louis I Landau, Principal Medical Advisor, Medical Workforce, Department of Health

**DEVELOPMENTAL PATHWAYS PROJECT**

ARACY New Investigator Network, National Collaboration  
 Dr Natasha Pearce, Edith Cowan University  
 Dr Laura Thomas, Edith Cowan University  
 Assoc Prof Leah Bromfield, Australian Centre for Child Protection, University of South Australia, Adelaide, Australia

Prof Marni Brownell, University of Manitoba, Manitoba Centre for Health Policy, Canada  
 Prof Jane Fisher, The Jean Hailes Foundation, Monash University, Victoria, Australia  
 Prof Ruth Gilbert, University College London, Institute of Child Health, United Kingdom  
 Dr Steven Guthridge, Department of Health and Community Services, Northern Territory, Darwin, Australia  
 Dr Daryl Higgins, Australian Institute of Family Studies, Melbourne, Australia  
 Dr Melissa Kaltner, Queensland Health, Brisbane, Australia  
 Dr Kirsten McKenzie, Queensland University of Technology, Brisbane, Australia  
 Debbie Scott, Australian Institute of Family Studies, Melbourne, Australia

## HUMAN CAPABILITY

Martin Cooke (University of Waterloo, Waterloo, Ontario, Canada) and David Povah and Elena Mobilia (Australian Bureau of Statistics, Perth).  
 Linda Harrison, Charles Sturt University, Bathurst.  
 Megan Shipley, Department of Families, Housing, Community Services and Indigenous Affairs, Canberra.  
 Ben Edwards, Australian Institute of Family Studies.  
 David Zarb (Playgroup WA Inc.), Donna Berthelsen (Queensland University of Technology) and Jan Nicholson (Parenting Research Centre; Murdoch Childrens Research

Institute).

Sybill McKeown, Glen Draper, Bufton & Jackson (Australian Bureau of Statistics), Geoff Davis & Di Rosman (WA Department of Health), and Daniel McAullay (Aboriginal Health Council of WA).

Rebecca Giallo, Fabrizio D'Esposito, Mensah, Cooklin, Wade, Lucas, Canterford, and Nicholson (Parenting Research Centre).

Sandra Eades (University of Sydney), and Bridgette McNamara and Lina Gubhaju (Baker IDI Heart and Diabetes Institute).

Eugen Mattes, Keelan, Hickey (UWA).

Office of the State Coroner and Department of Forensic Pathology (PathWest), Perth.

Renee Goodwin, Columbia University.

Ryan Van Lieshout, McMaster University.

Rachel Skinner, University of Sydney.

David Burgner, Murdoch Childrens Research Institute.

Fiona Armstrong, Climate and Health Alliance, Victoria.

Professor Maurice B. Mittelmark, University of Bergen, Norway.

## INFECTIOUS DISEASES GROUP

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Bega Garnbirringu Health Services, Kalgoorlie WA

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The Children's Hospital at Westmead.

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Dr Carolyn Ellaway, Children's Hospital, Westmead, NSW.

Prof Elizabeth Elliott, Paediatrics & Child Health, Children's Hospital, Westmead, FASD Collaboration.

Katheryn Frame, The International Foundation for CDKL5 Research, USA.

Dr Michael Freiling, University of Vienna, Austria.

Prof Sue Fyfe, Faculty of Health Science, Curtin University, Perth.

Prof Elizabeth Geelhoed, School of Population Health, UWA.

Dr Mika Gissler, THL National Institute for Health and Welfare, Helsinki, Finland.

Dr Raz Gross, Columbia University, New York, USA.

Ronnie Hagan, Department of Neonatology, School of Women's and Infants' Health, UWA, Perth.

Dr Kylie Hill, School of Physiotherapy, Curtin University, Perth.

A/Prof Mady Hornig, Columbia University, New York.

Institute of Psychiatry, London, UK.

Julie Ireland, Down Syndrome WA

Biostatistics, Karolinska Institutet, Stockholm, Sweden.

Prof Walter Kaufmann, Center for Genetic Disorders of Cognition and Behavior, Kennedy Krieger Institute and Johns Hopkins University School of Medicine, Baltimore, UWA.

Gwynnyth Llewellyn, University of Sydney, Sydney.

Prof Nick Lennox, University of Queensland, Queensland.

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Dr Lakshmi Nagarajan, Department of Neurology, Princess Margaret Hospital, Perth.

Dr Natasha Nassar, Kolling Institute of Medical Research, University of Sydney.

Norwegian Institute of Public Health, Oslo, Norway.

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Dr Eric Parner, University of Aarhus, Denmark.

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University of Aarhus, Denmark.

Columbia University, New York, USA.



# VACCINE TRIALS GROUP

## Overview

During 2012 our new studies have included Dornase Alfa, which aims to reduce repeat surgery in children with grommets. This project is a good example of the bench to bedside approach to translational research, where work arising from Ruth Thornton's PhD has directly led to a novel intervention for treating this common problem in WA children. The current whooping cough epidemic has illustrated the importance of trying to protect young babies from severe disease and so it was pleasing to see we were able to continue the follow-up of children in the newborn whooping cough vaccine study looking at booster vaccination at 18 months of age, which will help provide important information on the need to reinstate the booster on our immunisation schedule. A number of important vaccine studies have also continued this year including the Dengue Fever, Human Papillomavirus, Respiratory Syncytial Virus (RSV), Meningococcal B, Ross River Virus and the WA Influenza vaccine effectiveness in young children (WAIVE) study. We continue to be impressed by the dedication and time commitment of everyone who participates in our studies.

Highlights from 2012 must include the ongoing success of the FAST study, which was initiated last year to monitor the safety of the Influenza vaccine in young children and was extended to include pregnant women this year and has provided reassuring information on safety of the vaccine in these at-risk populations. We also continue to be involved in the national vaccine safety surveillance through the PAEDs program as well as the WA Vaccine Safety Surveillance System which was recognised with an award by WA Health. These studies are sponsored by

the WA Health Communicable Disease Control Directorate who are important partners in our research. Ensuring vaccines remain safe in those who use them continues to have a high priority in our research activities

Finally VTG has continued to be actively involved in the areas of otitis media, vaccine safety, pneumococcal diseases such as pneumonia & meningitis and predicting infections in premature infants. We have established new collaborations with researchers at the University of Queensland and the Lung Institute of WA to study why some adults and children are particularly prone to recurrent chest infections and chronic lung disease. I would like to congratulate our staff members who have presented data at international conferences during 2012, published in high impact international journals and have also secured ongoing funding for this research. We would like to acknowledge the support of the PMH Foundation in both supporting our research through grants and funding for important laboratory equipment to enable us and other groups in the hospital to continue our research. This we have also seen the establishment of the Allegra Scafidas Pneumococcal laboratory with the generous support of the Scafidas family and the Foundation they have set-up in memory of their daughter who died of pneumococcal meningitis. The lab is already starting to develop a national reputation and is now being utilised by local and interstate researchers. Using specialised equipment we have established several assays to perform our pneumococcal research work that are unique in Australia. We are now able to measure antibodies against the 13 different strains of the pneumococcus in a

single drop of blood. We can measure antibodies against vaccines (to see whether the vaccine produced protective antibodies) but also against other parts of the pneumococcus (proteins) as well as other bacteria to investigate whether children have been exposed to the bacteria and whether they might be useful to develop a protein based vaccine that would protect against all pneumococcal strains.

Thank you to our staff here at VTG, PMH, CDCD, Pathwest, UWA School of Paediatrics and Child health, Telethon Institute for Child Health Research and the families and children who are helping us to improve the health of our community.

## Immunisation

### MEN B 2001 STUDY FOR 11-18 YRS

PETER RICHMOND, SUB-INVESTIGATORS DR TANYA STONEY, DR GABRIELA WILLIS

A Randomised, Single- Blinded, Placebo - Controlled, Phase 2 Trial of the Safety, Immunogenicity and Tolerability of Meningococcal Serogroup B rLP2086 Vaccine at Doses of 60mcg, 120mcg and 200mcg. STAGE 1: 77 Subjects enrolled. STAGE 2: 120mcg, 200mcg & placebo dose cohorts for ongoing safety and immunogenicity evaluation. 33 Subjects enrolled. LSLV will occur in early 2014. Currently in the 4<sup>th</sup> year of follow up.

*Funders of the project*  
*Sponsored by Pfizer*

### PERTUSSIS AT BIRTH STUDY

DR NICK WOOD, SUB-INVESTIGATORS A/PROF

PETER RICHMOND, DR TANYA STONEY, DR GABRIELA WILLIS

Stratified, randomised but not blinded study. Aim to investigate if a monovalent Pertussis vaccine given at birth versus vaccination 6 weeks of age is safe and effective in protecting against Pertussis. To see if maternal dTpa in the previous 5 years influences infant Ab or CMI responses. 97 subjects recruited from Family Birth Unit at Mercy Hospital. LSLV was in Nov 2012. This study is completed at Vaccine Trials Group and is awaiting close out monitoring visit.

*Funders of the project*  
*Non-Sponsored - Funded by NH&MRC*

### PA AT BIRTH BOOSTER STUDY (PERTUSSIS AT BIRTH FOLLOW-ON STUDY)

DR NICK WOOD, SUB-INVESTIGATORS A/PROF PETER RICHMOND, DR TANYA STONEY, DR GABRIELA WILLIS

Participants in this study are aged 18 months to <24 months and must have completed participation in the Pertussis at Birth Study. This is a follow-on study from Pertussis at Birth study. The Birth Pertussis Booster Study is stratified, randomised and observer blinded. The study aims to determine persistence of immunity and response to a booster dose of standard dose DTPa or reduced dose dTpa at 18 months old following acellular pertussis vaccine given at birth. The recruitment target at Vaccine Trials Group is 50 subjects. The first subject's first visit was on 19 October 2012.

*Funders of the project*  
*Non-Sponsored - Funded by NH&MRC*

**A PHASE III, OPEN, RANDOMIZED, CONTROLLED, MULTI-CENTRE STUDY TO DEMONSTRATE THE NON-INFERIORITY OF THE MENINGOCOCCAL SEROGROUP C AND THE HAEMOPHILUS INFLUENZAE TYPE B IMMUNE RESPONSE OF GLAXOSMITHKLINE (GSK) BIOLOGICALS' CONJUGATE HIB-MENC VACCINE CO-ADMINISTERED WITH GSK BIOLOGICALS' MEASLES-MUMPS-RUBELLA VACCINE, PRIORIX™, VERSUS MENC-CRM197 CONJUGATE VACCINE CO-ADMINISTERED WITH GSK BIOLOGICALS' HIB VACCINE, HIBERIX™, AND PRIORIX™ IN 12- TO 18-MONTH-OLD TODDLERS PRIMED IN INFANCY WITH A HIB VACCINE BUT NOT WITH A MENINGOCOCCAL SEROGROUP C VACCINE; AND TO EVALUATE THE LONG-TERM ANTIBODY PERSISTENCE UP TO 5 YEARS AFTER THE ADMINISTRATION OF THE HIB-MENC VACCINE.**

ASSOCIATE PROFESSOR PETER RICHMOND

Vaccine Trials group have been involved in this multi-centre trial with 5 other sites in Australia. In this open, controlled trial, toddlers between 12 and 15 months of age were randomised 3:1 into 2 groups – to receive a combined HibMenC vaccine or to receive the Hib and MenC vaccines separately, when co-administered with the MMR vaccine. Safety data was collected and blood samples were taken one month post vaccination. Follow up visits have been conducted yearly for the past 5 years where blood samples have been

collected.

The inclusion criteria was healthy toddlers who were primed with a Hib containing vaccine in infancy but were MenC naive. A total of 433 children were enrolled with the Vaccine Trials Group recruiting 49 subjects for this study.

Co-primary objective – To show that the combination HibMenC vaccine was non-inferior to the Hib and MenC vaccines given separately

Secondary objectives – For 5 years post vaccination the persistence of AB levels were to be measured. Also to evaluate the safety of the vaccine.

We have now completed all the follow up visits for this study and due to the results of this trial the combination HibMenC vaccine (trade name Menitorix) had been licensed in Australia and will be on the Australian Immunisation Schedule for toddlers at 12 months of age from July 2013.

*Funders of the project.*  
*GlaxoSmithKline*

**LOT-TO-LOT CONSISTENCY AND BRIDGING STUDY OF A TETRAVALENT DENGUE VACCINE IN HEALTHY ADULTS IN AUSTRALIA**

ASSOCIATE PROFESSOR PETER RICHMOND

Dengue is a disease caused by a 4 types of a virus that is transmitted by mosquito bites. People who catch the dengue virus may get “dengue fever” – fever up to 40°C for 2 to 7 days, often with severe headache, vomiting, muscle and joint pains, pain behind the eyes, and skin rash. Dengue is sometimes more severe and can cause bleeding and/or a sudden fall in

blood pressure (shock). Dengue can cause death in some cases, mainly in children.

There are no vaccines and no specific treatments presently available against the disease.

The purpose of this research study is to see if four different batches of the study vaccine produce a similar antibody response and to continue to assess the safety of the vaccine.

Recruitment for this study commenced in October 2010 and 74 subjects were recruited to this site. The study was completed in October 2012.

*Funders of the project - Sanofi Pasteur SA*

**A PHASE III, DOUBLE-BLIND, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE SAFETY, IMMUNOGENICITY AND EFFICACY OF GLAXOSMITHKLINE BIOLOGICALS' HPV 16/18 L1/AS04 VACCINE ADMINISTERED INTRAMUSCULARLY ACCORDING TO A THREE-DOSE SCHEDULE (0, 1, 6 MONTH) IN HEALTHY ADULT FEMALE SUBJECTS AGED 26 YEARS AND ABOVE.**

DR TANYA STONEY AND ASSOCIATE PROFESSOR RACHEL SKINNER

Human papilloma viruses (HPV) are viruses that cause a common infection of the skin and genitals in men and women. Several types of HPV infection are transmitted by sexual contact and, in women, can infect the cervix (the lower part of the uterus or womb). This infection often goes away by itself. However, if it does not go away (this is called persistent infection), it can lead over a long period of time to cancer of the

cervix. If a woman is not infected by HPV, it is very unlikely that she will get cervical cancer. Two types of HPV, called HPV-16 and HPV-18, cause about 70 percent of the cases of cervical cancer in the world. Consequently, a vaccine able to prevent HPV infections would be of great value in the protection against cervical cancer.

GSK Biologicals has developed a vaccine against HPV types 16 and 18. This HPV vaccine has been tested in thousands of young women in different countries, and the reactions observed with the injection of the vaccine to date have been similar to those seen after vaccination with other common vaccines. These studies have also shown that the vaccine stimulates defences against the viruses, e.g. production of antibodies (substances made by your body to prevent infections). It has also been shown that the vaccine prevents persistent infections with HPV-16 or -18 and associated pre-cancerous abnormalities (this is called vaccine “efficacy”). Although pre-teen and adolescent girls represent an important target population for preventive HPV vaccination, vaccination should also be made available to adult women. This study is therefore designed to evaluate the immune responses, safety and efficacy of the investigational HPV vaccine in women who are 26 years of age or older.

The seventh year of the Cervarix HPV vaccine trial for women aged over 26 years commenced in 2012. One hundred and fifty women were recruited into this study at VTG. The purpose of this study is to determine the efficacy, safety and immunogenicity of Cervarix in older women. Currently the HPV-16/18 vaccine (*Cervarix*) is licensed in over 100 countries world wide, and is offered free to young women in HPV vaccination

programs in the UK and some other European countries. Cervarix was licensed in Australia in May 2007; however it is still important that the current studies are completed to determine the efficacy of the vaccine in older women which can then be used for cost effectiveness modelling.

*Funders of the project – GlaxoSmithKline*

### A PHASE IIIB, OPEN, MULTI CENTRE GYNAECOLOGICAL EXTENSION STUDY FOR FOLLOW-UP OF A SUBSET OF 580299/008 STUDY SUBJECTS WHO WERE EITHER CERVICAL CYTOLOGY NEGATIVE AND ONCOGENIC HPV POSITIVE OR PREGNANT AT THEIR FINAL 580299/008 STUDY VISIT (VISIT 10 AT MONTH 48).

ASSOCIATE PROFESSOR RACHEL SKINNER

This study is an extension of the HPV-008 research study with GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine for healthy females 15 – 25 years of age. This study offered women additional gynaecological follow-up if they were shown to have a positive oncogenic HPV infection although their cervical cytology test was normal at their last HPV-008 study visit. In addition, a woman who was pregnant at her last HPV-008 study visit and no cervical sample was taken, was also eligible to enter. Nineteen women were eligible to participate in this study which began in 2009 and was completed in 2012.

*Funders of the project - GlaxoSmithKline*

### A PHASE IIIB, OPEN-LABEL, MULTI-CENTRE IMMUNIZATION

### STUDY TO EVALUATE THE SAFETY OF GLAXOSMITHKLINE (GSK) BIOLOGICALS' HPV-16/18 L1 VLP ASO4 VACCINE ADMINISTERED INTRAMUSCULARLY ACCORDING TO A 0, 1, 6-MONTH SCHEDULE IN HEALTHY FEMALE SUBJECTS WHO RECEIVED THE PLACEBO CONTROL IN THE GSK HPV-015 STUDY.

DR TANYA STONEY AND ASSOCIATE PROFESSOR RACHEL SKINNER

This study is an extension of the HPV-015 research study with GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine for healthy females over 26 years of age. Currently the HPV-16/18 vaccine (Cervarix) is licensed in over 100 countries world wide, and is offered free to young women in HPV vaccination programs in the UK and some other European countries. Cervarix was licensed in Australia in May 2007 for women up to the age of 45 years. This study allows women over the age of 45 years, who have participated in the HPV 015 study, to have access to the vaccine if they have not already had it during the course of the study. This study is ongoing.

*Funders of the project - GlaxoSmithKline*

### A PHASE 3 STUDY TO ASSESS THE IMMUNOGENICITY, SAFETY AND CONSISTENCY OF LOT MANUFACTURE OF ROSS RIVER VIRUS VACCINE IN HEALTHY MALE & FEMALE SUBJECTS 16YRS OF AGE AND OLDER.

ASSOCIATE PROFESSOR PETER RICHMOND

Ross River virus is a mosquito-borne virus

that causes Ross River Virus Disease (RRVD) in humans. Ross River is endemic and enzootic in Australia, Papua New Guinea, adjacent Indonesia and the Solomon Islands. In the past 10 years RRVD has been most prevalent among adults aged 25 and 39 and does not display a clear sex effect.

Subjects were divided into two age strata; Stratum A -1800 subjects aged 16 to 59 yrs and stratum B - 210 subjects aged 60 and over. A subset of approximately 1140 subjects in stratum A and all subject in stratum B were included in the immunogenicity evaluation.

The study involved six clinic visits with three vaccinations and 2 follow phone calls. Those subjects that were in the immunogenicity group had a blood draws at each visit. Subjects were asked to complete diary cards to capture injection site reactions, systemic adverse events and other AE's.

Recruitment for this study commenced in April 2011with 114 subjects recruited at this site. There are a total of six sites in Australia. The last subject last visit was completed in October of 2012.

*Funders of the project - Baxter*

### OPEN-LABEL PHASE 3B STUDY TO ASSESS THE SAFETY OF ROSS RIVER VIRUS (RRV) VACCINE FROM 6 TO 12 MONTHS AFTER THE THIRD VACCINATION IN HEALTHY ADULTS (FOLLOW UP TO STUDY 880802)

ASSOCIATE PROFESSOR PETER RICHMOND

Aim of study is to extend the safety follow up period to 12 months after the third vaccine

received in the 880801 study, focusing on serious adverse events (SAE) and adverse events of special interest (AESI)

Eighty four participants from the 880801 study enrolled in this safety follow up study.

The last clinic appointment for this study is due to occur in March 2013

*Funders of the Study: Baxter*

### A PHASE 3, RANDOMIZED, COMPARATIVE, MULTICENTER OBSERVER-BLIND STUDY EVALUATING THE SAFETY AND IMMUNOGENICITY OF NOVARTIS RMENB+OMV NZ VACCINE FORMULATED WITH OMV MANUFACTURED AT TWO DIFFERENT SITES, IN HEALTHY ADOLESCENTS AGED 11-17 YEARS

ASSOCIATE PROFESSOR PETER RICHMOND

The meningococcal B vaccine study was conducted in Australia and internationally to compare 2 batches of the same vaccine manufactured at 2 different sites. The study was conducted to see if the Men B vaccines are safe and effective in adolescents. It is hoped that the vaccines produced at two different manufacturing sites will produce the same antibody responses in the study participants.

The Vaccine Trials Group has enrolled 12 participants into the study. Participants attended Vaccine Trials Group for 3 visits over 2 months. They were vaccinated at visits 1 and 2, and blood sample was collected at visits 1 and 3. A diary card was completed by participants after each vaccination.

The study was completed in February 2012. This vaccine has since been licensed in the Europe and it is expected that this vaccine will be licensed in Australia within the next 12 months.

## Surveillance

### A PROSPECTIVE COHORT STUDY OF MOTHER-INFANT PAIRS ASSESSING THE EFFECTIVENESS OF MATERNAL INFLUENZA VACCINATION IN PREVENTION OF INFLUENZA IN EARLY INFANCY.

ASSOCIATE PROFESSOR PETER RICHMOND

The primary aim of the FluMum Study is to determine the effectiveness of maternal influenza vaccine in pregnancy against laboratory confirmed influenza among infant offspring during the first 6-months of life. Also while conducting this study we aim to;

- Establish the first national system of validated annual influenza vaccine uptake in pregnancy.
- Monitor annual changes in vaccine uptake over time within each of the participating sites.
- Assess the factors that influence the decision to receive influenza vaccination during pregnancy and examine why women are not being vaccinated in pregnancy.
- Estimate the effectiveness of maternal influenza vaccine in pregnancy against laboratory confirmed influenza in the mother during pregnancy and hospitalization of the infant with acute lower respiratory infection (ALRI) during the

first six months of life.

10,106 mother-infant pairs will be recruited in six study sites (Darwin, Brisbane, Sydney, Melbourne, Adelaide and Perth) over four consecutive influenza seasons (2012-2015). Assuming equivalent recruitment rates, this will equate to 421 mother-infant pairs per site per year.

*Funders of the project.*

*This is a National Health and Medical Research Council Project Grant.*

### THE CHILDREN'S WESTERN AUSTRALIAN INFLUENZA VACCINE EFFECTIVENESS (WAIVE) STUDY

A/PROF DR PETER RICHMOND, A/PROF DR CHRIS BLYTH, DR DALE CARCIONE, DR GABRIELA DIXON, DR PAUL EFFLER, A/PROF GARY GEELHOED, DR ANTHONY KEIL, DR HEATH KELLY, DR ALAN LEEB, HANNAH MOORE, DR DAVID SMITH, DR PAUL VAN BUYNDER, AVRAM LEVY, PETER JACOBY

To assess the effectiveness of the trivalent influenza vaccine in young children (full and partially vaccinated) and to assess the burden of influenza in young children and their families

We recruit children aged between 7mths and 5years who present to Princess Margaret Hospital for Children Emergency Department & hospital inpatients with an influenza like illness(ILI)

During the 2012 influenza season we recruited a total number of 832 subjects. Of these, 682 children were recruited through the Emergency Department, and 150 were recruited through hospital admission to the wards.

Even though the recruitment numbers were high for 2012, uptake of the influenza vaccine for under five year olds was still very low, only 9% of children recruited into WAIVE in 2012 were vaccinated for influenza. This is still likely to be due to the adverse events associated with the CSL Fluvax brand influenza vaccine given in 2010 which caused an increase in high fever and febrile convulsions.

In the peak of the 2012 flu season approximately 40% of children recruited, tested positive for influenza.

*Funders of the project*

*Communicable Disease Control Directorate, Department of Health WA*

### PAEDIATRIC ACTIVE ENHANCED DISEASE SURVEILLANCE - PAEDS

RICHMOND P, BLYTH C, PHILLIPS A, RHIND L, ELLIOT E, ZURYNSKI Y, PYM M, MCKAY N, MCINTYRE P, BOOY R, WOOD N, DEEKS S, ROYLE J, BUTTERY J, ELIA S.

PAEDS is coordinated by the Australian Paediatric Surveillance Unit (APSU) and the National Centre for Immunisation and Surveillance of Vaccine-Preventable Diseases (NCIRS). There are currently four sites involved across Australia:

- Princess Margaret Hospital for Children (PMH), Perth
- Women's and Children's Hospital, Adelaide
- Royal Children's Hospital, Melbourne
- The Children's Hospital at Westmead, NSW

PAEDS objective is to test the value of hospital-

based active surveillance for identifying and investigating childhood conditions of public health importance which are difficult to adequately capture through other surveillance mechanisms.

The four conditions currently included as surveillance studies are: Acute Flacid Paralysis (AFP), Intussusception (IS). Severe Varicella (VZV) and Pertussis (Pert)

Cases screened and recruited at PMH from 1.1.2012 – 31.12.2012

AFP - 125 cases of AFP screened and 5 recruited with 40% stool sample collection

IS - 311 cases of IS screened and 27 recruited (1 confirmed case, consent not obtained)

VZV (Severe hospitalised) - 313 cases screened and 4 recruited

Pertussis – 700 cases screened – 21 cases laboratory confirmed positive for pertussis, 6 consented, 19 consent not obtained

*Funders of the project*

*Commonwealth Dept of Health & Ageing*

### ROTAVIRUS AND GASTROENTERITIS SURVEILLANCE STUDY (RAGS)

A/PROF DR PETER RICHMOND, DR PAUL EFFLER, DR DALE CARCIONE, PROF DAVID FORBES,

A/PROF GARY GEELHOED, DR GERALD HARNETT, DR ANTHONY KEIL, A/PROF CARL KIRKWOOD, PROF TOM RILEY, DR DAVID SMITH, DR MICHAEL WATSON, SIMON WILLIAMS,

To assess the effectiveness of Rotavirus vaccine on community acquired Rotavirus presenting to ED and hospital inpatients and also to assess

the impact of the infant rotavirus immunisation program on rotavirus genotypes circulating in the community

We recruit children presenting to the Princess Margaret Hospital for Children (PMH) emergency department or admitted to the medical ward with acute gastroenteritis under the age of 5 years and who have a history of at least 3 episodes of diarrhoea within 24 hour period

In 2012 there were a total of 73 subjects recruited, with 75% of children being vaccinated for Rotavirus. There were 58 stool samples collected, of these seven children tested positive for rotavirus, 5 x children had been vaccinated for rotavirus and 2 children had not been vaccinated.

*Funders of the project  
Department of Health WA*

## FEBRILE SEIZURES: VIRAL INFECTIONS AND THEIR ETIOLOGIC ROLE (FEVER)

DR JOSH FRANCIS, A/PROF CHRIS BLYTH, A/PROF PETER RICHMOND, DR PAUL EFFLER, CHRISTINE ROBINS, DR GARY GEELHOED, DR TRACY MARKUS, DR ANDREW CURRIE, AVRAM LEVY, DALE CARCIONE, MELISSA CHANTRY

This is a prospective study investigating the role of viral infections in febrile seizures. The aims of the study are to determine the incidence of specific viral pathogens in children presenting with febrile seizures and to describe the risk factors and clinical features associated with specific pathogens in children presenting with febrile seizures.

A total of 150 patients are required and to date

there have been 88 subjects recruited. Data for the 88 enrolled subjects is only preliminary at this stage, and does not include results of virological testing, which are still pending. Due to workflow issues in the laboratory related to seasonal changes in epidemiology, study samples will be tested in batches. Results are anticipated in the near future, and preliminary analysis of the first 88 patients will be possible at that time.

*Funders of the project  
Department of Health WA*

## THE WESTERN AUSTRALIAN CHILDREN'S FOLLOW UP AND ACTIVE SURVEILLANCE OF TRIVALENT INFLUENZA VACCINE (FAST) STUDY

A/PROF. PETER RICHMOND, A/PROF. CHRISTOPHER BLYTH, DR TRACY MARKUS

To detect any significant increase in seasonal trivalent inactivated influenza vaccine (TIV) related febrile reactions and/or any other adverse events following immunisation (AEFI) with seasonal TIV and to provide active surveillance of seasonal TIV associated adverse events and provide timely feedback to healthcare consumers re: rate of TIV associated adverse events.

Due to low uptake of influenza vaccination in 2012 there were 277 children recruited. Significant adverse-events including fever following TIV were not observed in children who received the 2012 formulation of Vaxigrip and overall rates of any reaction were low.

*Funders of the project  
Communicable Disease Control Directorate,*

*Health Protection Group, Western Australian  
Department of Health (WA DoH)*

## Infectious Diseases

### DYNAMICS OF HAEMOPHILUS HAEMOLYTICUS AND NONTYPEABLE HAEMOPHILUS INFLUENZAE COLONISATION IN OTITIS-PRONE CHILDREN

DR LEA-ANN KIRKHAM AND DR SELMA WIERTSEMA

Otitis media (middle ear infection, OM) is a common childhood upper respiratory tract illness, responsible for the greatest number of GP visits, antibiotic prescriptions, and surgical operations for children in industrialised countries. Approximately 2 million children suffer from OM in Australia each year. The health, social and financial costs of OM to Australia are substantial with treatment alone estimated to cost \$100-400 million/year. In Australia, the bacterium nontypeable *Haemophilus influenzae* (NTHi) is the predominant cause of OM. A vaccine (Synflorix®) has been licensed in Australia, and is used in 9 other countries, which has the potential to reduce the burden of OM. Accurate surveillance of the impact of this vaccine is hampered by another bacterium, *H. haemolyticus* (Hh), which masquerades as NTHi and cannot be distinguished using standard techniques. This has resulted in inaccurate surveillance. We are developing sensitive and specific molecular assays to accurately identify NTHi and Hh. These assays will be important for studies assessing the impact of Synflorix vaccination and other new OM-targeted vaccines.

*Funder of the project - National Health and  
Medical Research Council (NHMRC).*

### EVALUATION OF ANTIBODY LEVELS AND FUNCTION IN OTITIS-PRONE AND HEALTHY AUSTRALIAN CHILDREN

DR LEA-ANN KIRKHAM, DR SELMA WIERTSEMA, DR RUTH THORNTON AND DR PETER RICHMOND

We and others have shown that children with ear infections (OM) have good antibody responses to the bacteria that cause OM. However, these children still get recurrent OM infections. This raises two important questions:

1. is the immune response actually doing what it is meant to do and
2. is the immune system doing this at the right site, i.e. in the middle ear

To answer these questions we are using blood, saliva and middle ear fluid samples that we collected from children with OM. This work will give insight into the role of the immune system in the development of OM and will contribute to advanced prevention and treatment strategies for OM.

*Funders of the project - National Health and  
Medical Research Council (NHMRC) and Princess  
Margaret Hospital Foundation.*

### DISSOLVING THE GLUE IN GLUE EAR: ASSESSMENT OF THE USE OF DORNASE ALFA AS AN ADJUNCT THERAPY TO VENTILATION TUBE INSERTION.

R. THORNTON, P. RICHMOND, H. COATES, S. VIJAYASEKARAN AND P. JACOBY.

Grommet insertions for middle ear infections are the second most common reason for preschool children to undergo surgery. Up to one third of these children will need to have repeat surgeries due to infection recurrence. We believe the recurrence of otitis media is due to the presence of bacteria in “slime” which is known as biofilm. Biofilm protects bacteria from the body’s immune responses and makes bacteria up to 1000 times more resistant to antibiotics. These biofilm structures need to be broken down to make treatments work. We have shown that biofilms can be found within DNA net-like structures in the middle ear fluid. These DNA structures are largely produced by cells of the immune system known as neutrophils. This is similar to what is seen in the lung fluid from patients with cystic fibrosis.

We believe that these DNA nets form the “glue” in the middle ear and behave like the sticky fluid in the lungs of children with cystic fibrosis. This stops the body from getting rid of the bacteria and acts as a site where bacteria are able to grow and reinfect the ear. We believe that these DNA nets represent a treatment target to reduce the number of complications and ear infections following grommet surgery. Breaking down this glue will also make the bacteria more susceptible to the body’s protective responses.

In the laboratory we have shown that in a test tube, a treatment commonly used in cystic fibrosis treatment (Pulmozyme® or Dornase alfa) is able to break down the sticky “glue” from the ears of children with chronic and recurrent middle ear infections. We believe that this has practical applications in treating middle ear

infections and lowering the rate of infection recurrence following grommet insertion.

In this study we have been trialling the use of Dornase alfa at the time of grommet insertion to break down the “glue” in the middle ear to allow for more effective clearance of bacteria from this site and to increase the effectiveness of the antibiotic drops which are commonly used.

We have now enrolled 20 subjects into this study. The results from these first 20 subjects are being reviewed by the Data Safety Monitoring Board before continuing enrolment early in the 2013. We hope to enrol 60 subjects overall into this trial.

*Funders of the project - Western Australian Government State Health Research Advisory Council and PMH Foundation.*

## NEWBORN INFECTION AND IMMUNITY (PREDICT STUDY)

DR ANDREW CURRIE, DR TOBIAS STRUNK

Preterm infants (>22,000/year in Australia) are particularly prone to infections with commensal microorganisms, such as coagulase negative staphylococci, which rapidly colonise all newborns after birth. Additionally, preterm infants have worse outcomes from infections with more pathogenic organisms such as Escherichia coli and Candida albicans. As defence against infection in the newborn is critically reliant on the innate immune system, detailed comparison of preterm and term infant responses to various microorganisms will allow characterisation of the key innate responses that normally recognise and control both commensals and pathogens in healthy infants

and children. We have established a number of clinical studies which give us unique access to preterm and term infant samples, both at birth (cord blood) and during early life and childhood, when the risk of infection is highest. Using these cohorts we are trying to:

1. Identify critical innate immune pathways of newborn commensal and pathogen recognition
2. Study the development of the innate immune system in infancy and early childhood
3. Examine the impact of antenatal factors (such placental inflammation) on innate immune function
4. Determine if innate responses in the newborn are epigenetically regulated

*Funders of the project - Health and Medical Research Council (NHMRC), BrightSpark Foundation Inc, PMH Foundation, European Society of Infectious Diseases*

## ROLE OF BACTERIAL BIOFILM AND INTRACELLULAR INFECTION IN CHRONIC AND RECURRENT OTITIS MEDIA

ASSOCIATE PROFESSOR PETER RICHMOND, H. COATES, S. VIJAYASEKARAN AND R. THORNTON

While more than 80% of children will experience at least one ear infection (OM) episode by three years of age, 33% will experience three or more episodes by this same age. Increases in children who suffer from recurrent OM have been observed and antibiotic treatment in these children is often ineffective. Our work has shown

that the bacteria which cause these infections can be found in a ‘slime’ or biofilm on the skin in the middle ears of children. When bacteria are in this slime they are seen to be up to 1000 times more resistant to antibiotics than the ‘free floating’ bacteria which make the children sick. They also allow the bacteria to be shielded from the body’s own response meaning that when the antibiotics are finished the bacteria can again become free floating and cause an infection.

We have also shown that as well as been in slime, these bacteria can live inside the cells of the middle ear, the problem with this being that when they survive inside the cell they are again largely protected from the antibiotics that are commonly used to treat this infection as well as the body’s own immune response. Whether is biofilm or intracellularly, these bacteria represent an infectious reservoir from which they can cause reinfection giving rise to what we see in some children who always seem to have glue ear or infections.

These findings are very important as it leads us to explore new treatment options that will hopefully be more effective at targeting these infectious reservoirs and preventing chronic and recurrent infections in the future.

*Funder of the project - PMH Seeding grant, Garnett Passe and Rodney Williams Foundation.*

## MECHANISMS OF BACTERIAL PERSISTENCE AND POTENTIAL FOR VACCINATION IN PATIENTS WITH COPD.

P. RICHMOND, R. THORNTON, S. WIERTSEMA AND L. KIRKHAM.

Chronic obstructive pulmonary disease (COPD) is a broad term used to describe chronic lung disease that includes bronchiectasis, chronic bronchitis, chronic asthma and emphysema. COPD is the fourth most common global cause of adult death with symptoms including a chronic productive cough, shortness of breath, wheezing and frequent acute infectious exacerbations.

Acute exacerbations of COPD have been clearly associated with isolation of respiratory bacteria, particularly nontypeable *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*, from sputa at the time of exacerbation. These recurrent exacerbations result in a worsening of the patient's condition, which usually requires additional treatment and significantly increases mortality rates.

We propose that the cause of recurring bacterial infection in patients with chronic lung disease (COPD) is that bacteria are not cleared from the lung, either by antibiotics or by the host's immune system. We have preliminary evidence that the bacteria survive and persist in the lung in superstructures known as biofilms, which are made up of bacteria surrounded by host and bacterial DNA and proteins. Bacteria residing in a biofilm are resistant to antibiotics and cannot be eliminated by the immune system. When conditions for the bacteria become favourable they can be released from the biofilm and replicate, thereby causing recurring acute infections. This study will confirm whether bacteria survive in biofilms in the lungs of patients with COPD and which species are involved. By understanding how bacteria persist in the lung of these patients we will be able to investigate alternative treatments, such as anti-

biofilm agents that allow antibiotics to eradicate the released bacteria. We will also measure the immune response of patients with COPD to investigate whether they are likely to benefit from new and developing protein vaccines that could reduce the incidence of lung infections.

*Funder of the project - Westcare.*

## Laboratory

### GENERIC BANK FOR PERIPHERAL BLOOD MONONUCLEAR CELL (PBMC) AND SERUM TO LOOK AT IMMUNOLOGY RESPONSES TO ALLERGENS, BACTERIA AND VACCINE ANTIGENS

PETER RICHMOND

This Bank has been established by VTG for research staff and students to access PBMC's for their own research projects.

Research projects are quite varied.

This study seeks to establish a bank of peripheral blood mononuclear cells (PBMC's), plasma and serum for the in vitro analysis of adult immunology responses to allergens, bacterial, viral and vaccine antigens. The samples are obtained from healthy volunteers. To date there are 100 study participants enrolled. Throughout the year we replenish stocks of existing participants.

Recruitment is ongoing.

*Funders of the Project  
Investigator Initiated*

### PBMC PREPARATION FOR CMI

### TESTING IN GSK ANTIGEN SPECIFIC CANCER IMMUNOTHERAPEUTIC (ASCI) PROJECTS

(NYES01-AS15-MEL-001/112406)

OR

### PERIPHERAL BLOOD MONONUCLEAR CELL PREPARATION FOR CELL MEDIATED IMMUNITY TESTING IN GSK ANTIGEN SPECIFIC CANCER IMMUNOTHERAPEUTIC PROJECTS (NYES01-AS15-MEL-001/112406)

ASSOC. PROF. PETER RICHMOND

In 2012 the Vaccine Trials Groups (VTG) was a certified laboratory for the processing of peripheral blood mononuclear cells (PBMCs) for the GSK Antigen Specific Cancer Immunotherapeutic (ASCI) project NYES01-AS15-MEL-001/112406. This study explores the immune responses and holistic outcomes of immunotherapy on 8 cancer patients. The patients are followed up with 12 visits over a 5 year period. The clinical side to the study occurs at the Princess Alexandra Hospital in Queensland and the Cancer Clinical Trials Centre in Victoria. Blood is then flown to the VTG in Perth for processing where PBMCs are frozen and sent on to GSK for final analysis. In 2012 no blood samples were collected for processing.

VTG had to meet a variety of 'minimum quality assurance requirements' that GSK set to become a certified lab. In addition to this four laboratory personnel completed a 'dry run' where samples were processed and the PBMCs were sent to GSK for analysis, to determine if the operators and the methods used were adequate for the study. Due to the fact that 12 months had passed and no samples had been processed,

laboratory personnel were required to complete another 'dry run' to remain certified. This second dry run was performed in October 2012 by the same 4 laboratory personnel maintaining certification status.

*Funders of the project: GlaxoSmithKline.*

## Staff and Students

### HEAD OF DIVISION

Peter Richmond MB BS MRCP FRACP

Associate Professor, School of Paediatrics and Child Health, University of Western Australia

Consultant Paediatrician and Paediatric Immunologist, Princess Margaret Hospital for Children

Director, Child and Adolescent Health Research Network, Child and Adolescent Health Service

Head, Department of Clinical Research and Education, Child and Adolescent Health Services

Honorary Research Fellow and Director, Vaccine Trials Group, Telethon Institute for Child Health Research

Deputy Chair, Australian Technical Advisory Group on Immunization, Commonwealth Department of Health and Aging

### RESEARCH STAFF

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Karli Corscadden BSc (Hons)  
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Helen Currie Medical student  
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Camille Gibson BSc Environmental Health RM  
BSc Nursing  
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Jessica Hillwood Medical student  
Julia Inman Medical student  
Matthew James Medical student  
Jane Jones BSc (Hons) BScN DipHealth Sc  
Jan Jones BSc (Hons) DipEd  
Jennifer Kent DipN  
Lea-Ann Kirkham PhD BSc (Hons)  
Timothy Loy Medical student  
Justine Mackie Medical student  
Fiona MacDonald BSc RM RGN  
Lisa Montgomery  
Samantha Moore Medical student  
Jennifer Morrison RN RM  
Annemarie Naylor Grad Cert CTM  
Alison Roberts BSc Dip Health Sci  
Christine Robins EN  
Zakary Snelson Medical student  
Tanya Stoney MBBS Dip Child Health  
Rachel Skinner MBBS PhD FRACP  
Caroline Talbot EN

Ruth Thornton PhD BSc (Hons)  
Selma Wiertsema PhD MScBSc  
Verity Watt Medical student

## POSTGRADUATE STUDENTS

Angela Fuery BSc (Hons) PhD Candidate  
Emma DeJong BSc (Hons) PhD Candidate  
Janessa Pickering BSc (Hons) PhD Candidate  
Stephanie Trend BSc (Hons) PhD Candidate  
Divya Muthiah Honours Student  
Sherrianne Ng Honours Student

## RESEARCH SUPPORT

Rachel Mulholland Administration Officer

## THESES PASSED

D Muthiah, Honours

“Investigating antimicrobial peptide responses in preterm infants”

## Awards

Lea-Ann Kirkham *2012 WA Young Tall Poppy Science Award*

Emma de Jong *2012 Dean's Prize for Best in Show - Murdoch University Postgraduate Poster Day*

Janessa Pickering *2012 PMH Foundation PhD Supplementary Scholarship*

Stephanie Trend *2012 PMH Foundation PhD*

## Supplementary Scholarship

Peter Richmond, Christopher Blyth *2012 Director General's Award – Vaccine Safety Surveillance System*

Ushma Wadia, *Runner up Poster prize, PHAA Conference, Darwin 2012*

## External Committees

Peter Richmond, Member, Adelaide Women's & Children's Hospital Vaccine and Trials Unit Scientific Advisory Board 2007-present

Peter Richmond, Member, National Centre for Immunisation Research and Surveillance Scientific Advisory Board 2008-present

Peter Richmond, Member, Influenza Specialist Group 2009-present

Peter Richmond, Chair, Rotovirus vaccine (RV3) Phase 2 study, Data Safety Monitoring Board, Murdoch Children's Research Institute, Melbourne 2011-present

## NATIONAL

Peter Richmond, Deputy Chairperson, Australian Technical Advisory Committee (ATAGI), Commonwealth Dept. of Health and Aging. 2010 to present

Peter Richmond, Chair, ATAGI MMR-Varicella and Herpes Zoster Vaccine Working Party, 2006 – present

Peter Richmond, Member, ATAGI Pneumococcal Vaccine Working Party, 2007 –present

Peter Richmond, ATAGI Hib and meningococcal C

Vaccine Working Party, 2008 – present

Peter Richmond, Joint ATAGI and Therapeutic Goods Administration (TGA) Seasonal Influenza Vaccine Safety Ad Hoc Working Group 2010-12

Peter Richmond, Member NHMRC Grant Review Panel for Microbiology & Virology (GRP 2E) 2011-12

Peter Richmond, Member, Steering Committee PTNA (Paediatric Trials Network of Australia) 2010 to present

Christopher Blyth, Member: Australian Technical Advisory Group on Immunisations (ATAGI), Australian Government: Department of Health and Aging

Christopher Blyth, Member: ATAGI Influenza Working Party, Australian Government: Department of Health and Aging

Christopher Blyth, Member: ATAGI Pneumococcal Working Party, Australian Government: Department of Health and Aging

Christopher Blyth, Member: ATAGI Varicella / Zoster Working Party, Australian Government: Department of Health and Aging

## LOCAL

Peter Richmond, Chair, WA Immunisation Scientific Advisory Group, 2011-present

Peter Richmond, Member, Princess Margaret Hospital for Children Ethics Committee 2003-present

Peter Richmond, Chair, New Children's Hospital Research and Education Reference Group 2009-



201

Peter Richmond, Chair, Child Health Research and Education Advisory Committee, CAHS, 2009-present

Christopher Blyth, Member: WA Tuberculosis Advisory Council, Health Department of Western Australia

Christopher Blyth, Member: Expert Advisory Committee for Prevention and Control of Pertussis in WA, Communicable Disease Control Directorate, Health Department of Western Australia,

Christopher Blyth Member: Expert Advisory Committee on Pneumococcal Surveillance in WA, Communicable Disease Control Directorate, Health Department of Western Australia,

Christopher Blyth Member: Expert Advisory Committee for Influenza Vaccination, Communicable Disease Control Directorate, Health Department of Western Australia

## INVITED PRESENTATIONS

Janessa Pickering - Oral presentation: '*Modelling nasopharyngeal colonisation dynamics- can Haemophilus haemolyticus prevent NTHi infection?*'. Child and Adolescent Health Symposium, Perth, October 2012. Pickering, Janessa1,2,, Prosser, Amy1,2, Thornton, Ruth1,2, Richmond, Peter1,2,3, Kirkham, Lea-Ann1,2, 1School of Paediatric and Child Health, The University of Western Australia, 2Telethon Institute for Child Health Research, Centre for Child Health research, University of Western Australia, 3 Princess Margaret Hospital for Children, Perth, Australia.

Janessa Pickering - Oral presentation: '*Development of a real time PCR (RT-PCR) assay for the selective detection of Haemophilus haemolyticus, the respiratory tract commensal frequently misidentified as Nontypeable Haemophilus influenzae (NTHi)*'. Australian Society for Microbiology Conference, Brisbane 2012. Pickering, J1,2, Binks, MJ3, Smith-Vaughan, H3, Wiertsema, SP1,2, Kirkham, LA1,2. 1School of Paediatrics and Child Health, University of Western Australia, Perth, Australia, 2Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, Australia, 3Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Janessa Pickering - Oral presentation: '*Can the hpd gene target be used to discriminate the respiratory tract commensal Haemophilus haemolyticus, from the closely related pathogen Nontypeable Haemophilus influenzae?*' Australian Society of Medical Research symposium, Edith Cowan University, Perth, June 2012. Authors: Janessa Pickering1, Peter Richmond1,2,3, Lea-Ann Kirkham1,2 1School of Paediatrics and Child Health, University of Western Australia 2Telethon Institute for Child Health Research, Perth, WA 3Princess Margaret Hospital for Children, Perth, WA

Janessa Pickering - Oral presentation: '*The impact of Haemophilus haemolyticus on NTHi diagnosis and disease*'. OMOZ 2012 Conference, Esplanade Hotel Fremantle, May 2012.

Janessa Pickering1,2, Amy Prosser1,2, Lea-Ann Kirkham1,2, Peter Richmond1,2,3 1School of Paediatrics and Child Health, University of Western Australia, 2Telethon Institute for Child Health Research, Perth, WA, 3Princess Margaret

Hospital for Children, Perth, WA

Thornton R.B., Bacterial persistence mechanisms in the respiratory tract. Respiratory Medicine Rottneest Conference. November, 2012. (Invited Speaker) Perth, Western Australia.

Thornton,R.B., Wiertsema, S.P., Kirkham, L.S., Vijayasekaran, S. Coates, H.L. and Richmond, P.C., Dissolving the glue in glue ear: Assessment of the use of Dornase alfa as an adjunct therapy to ventilation tube insertion. The Second Australian Otitis Media Workshop, May, 2012, Perth, Western Australia.

Thornton, R.B. Battling bacterial slime: Bacterial persistence mechanisms in chronic and recurrent respiratory infections. Centre for Microscopy, Characterisation and Analysis Seminar Series, October, 2012. Perth, Western Australia.

Associate Professor Chris Blyth, Clinical and biological investigations into Trivalent Influenza Vaccination in 2010,

Associate Professor Chris Blyth, *Influenza Specialist Group Annual Scientific Meeting. Melbourne 2012*

Associate Professor Chris Blyth, Top 5 Mycology Papers, Australasian Society of Infectious Diseases Conference, Perth 2012

Associate Professor Chris Blyth, Influenza – What happened and how do we come back from 2010, Immunisation Update, Southern Country Health Service, Albany 2012

Associate Professor Chris Blyth, What we have learnt from influenza vaccination, Immunisation Update, Grace Vaughan House, 2012

Peter Richmond, Australasian Society for

Infectious Disease Annual Scientific Meeting, Perth, March 2012 (Invited Speaker, Session Chair)

Peter Richmond, Public Health Association of Australia 13<sup>th</sup> Immunisation Conference, Darwin, June 2012 (Invited Speaker)

Peter Richmond, OMOZ (Otitis Media) Conference, Perth, May 2012

Emma deJong , Oral presentation title: Understanding the Immunological Susceptibility to Gram-positive Infection in Preterm Infants

Emma deJong, Conference: Australian Society for Medical Research, Perth, 7-Jun-2012

Emma de Jong, Oral presentation title: Understanding the Immunological Susceptibility of Preterm Infants to Sepsis, TICHR Student Symposium, Perth, 20-Aug-2012

Emma de Jong, Poster presentation title: Characterising the Preterm Infant Monocyte Response to Gram-Positive Pathogens, Combined Biological Sciences Meeting, Perth, 24-Aug-2012

Emma de Jong, Poster presentation title: Characterising the Preterm Infant Monocyte Response to Gram-Positive Pathogens, Murdoch Postgraduate Poster Day, Perth, 9-Nov-2012

Andrew Currie, invited Speaker, Postnatal development of human innate immune defences in infants, King Edward Memorial Hospital Neonatal Summer Symposium, Australia, 2013

Andrew Currie, Invited Speaker, Day dot: Ontogeny of the human infant monocyte system, Bi-annual Meeting of the Australian TLR research Network (TLROZ), Australia, 2012

Andrew Currie, Speaker selected from abstract, Postnatal development of human innate immune defences in infants, Australasian Society for Immunology National Meeting, Australia, 2012 - (data presented from NHMRC project grant 572548)

## ACTIVE collaborations

The Children's Western Australian Influenza Vaccine Effectiveness (WAIVE) Study. A collaborative study between TICHHR, PMH, UWA, PathWest and CDCD

Rotavirus and Gastroenteritis Surveillance Study (RAGS). A collaborative study between TICHHR, PMH, UWA, PathWest and CDCD

The Western Australian Children's Follow up and Active Surveillance of Trivalent influenza vaccine (FAST) Study. A collaborative study between TICHHR, UWA, CDCD, PMH and Rheola Street

Febrile seizures: Viral infections and their Etiologic Role (FEVER). A collaborative study between TICHHR, UWA, CDCD, PMH

Examining Streptococcal pneumonia colonisation in young children in WA. A collaborative study between TICHHR, UWA, CDCD, PMH and Rheola Street

Paediatric Active Enhanced Diseases Surveillance (PAEDS). A collaborative study between TICHHR/UWA/PMH and NCIRS, Children's Hospital Westmead, Royal Children's Hospital Melbourne, Murdoch Children's Research Institute, Womens and Children's Hospital Adelaide, University of Adelaide, Royal Children's Hospital Brisbane

Linkage of the Australian Childhood

Immunisation Register (ACIR) and State-based Registered to Evaluate and Inform Australia's Immunisation Program. A collaborative study between TICHHR, UWA, NCIRS, Universities of Sydney, New South Wales and Western Sydney

Exploring Immunisation Uptake in High risk Groups. A early collaboration between TICHHR/UWA/PMH, Children's Hospital Westmead/NCIRS and Royal Children's Hospital Melbourne /MCRI

The Aetiology of Acute Lower Respiratory Tract Infection and Meningitis in Hospitalised Children from the Eastern Highlands Province, Papua New Guinea. A collaborative study between TICHHR, UWA, PMH, PathWest, PNGIMR and Goroka General Hospital

Defining host determinants of severe childhood pneumococcal pneumonia. A collaborative study between TICHHR, UWA, PNGIMR, Washington University and St Louis Children's Hospital

Australasian ID Physicians Survey. A collaborative study on behalf of the ASID Clinical Research Network

Exploring the pathogenesis of severe flu. A collaboration between TICHHR/UWA/PMH and University of Sydney/Westmead Hospital

Multidrug resistant tuberculosis in Australia. A collaboration WA Tuberculosis Control Program, Royal Perth Hospital, TICHHR, UWA and PMH.

# PUBLICATIONS

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4. Allen KL, McLean NJ, Byrne SM. Evaluation of a new measure of mood intolerance, the Tolerance of Mood States Scale (TOMS): Psychometric properties and associations with eating disorder symptoms. *Eating Behaviors*. 2012;13(4):326-334
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