



Telethon Institute for  
Child Health  
Research



# Celebrating 20 years

ANNUAL REPORT 2010 - SCIENTIFIC SUPPLEMENT



PRINCIPAL PARTNER



Telethon Institute for  
Child Health Research

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Throughout the past year, the Telethon Institute for Child Health Research has celebrated 20 years of service to improve and promote the health and wellbeing of all children through the unique application of multidisciplinary research.

From humble beginnings in the renovated nursing school at Princess Margaret Hospital, it is now the largest medical research facility in Western Australia, and one of the most significant in the nation.

Independent and not-for-profit, the Institute is home to more than 500 staff and postgraduate students and in the past year generated more than \$30 million in research funding.

This report not only outlines the highlights from the past year, but achievements over the 20 year period. It shows how Institute researchers have made significant discoveries and influenced policy to bring about substantial improvements in health and wellbeing for children in Australia and around the world.

## Our Mission

To improve and to promote the health and wellbeing of all children through the unique application of multidisciplinary research.

## Our Aims

- to conduct high quality research
- to apply research findings to improve the health of children, adolescents and families
- to teach the next generation of health researchers
- to be an advocate for research and for children



## Overview

Our research continues to focus upon the mechanisms underlying susceptibility versus resistance to respiratory infections and allergic diseases during childhood, and in particular how these mechanisms interact to drive asthma pathogenesis. Our long-term goal is to utilize this information to guide the development and testing of preventative treatments for asthma in early childhood, before the disease consolidates into its persistent form. In addition, we are expanding our research into the mechanisms underlying acute severe asthma attacks in children with established asthma, in particular how virus infections harness allergic responses to aid them in escaping attack by antimicrobial defences. We are continuing our research in areas related to pediatric vaccines, particularly those which protect against 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 which 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 speed of their functional maturation during the preschool years is retarded 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 which are responsible for immune surveillance in the respiratory tract. We are additionally expanding this experimental area to encompass viral infections and how these interact with and exploit allergic inflammatory mechanisms.

## Aetiology and pathogenesis of atopy and asthma

### ASSESSING RISK FOR ASTHMA DEVELOPMENT AMONGST INFANTS

P.G. Holt, J. Rowe, M. Kusel, F. Parsons, E.M. Hollams, A. Bosco, K.L. McKenna, L. Subrata, N.H. de Klerk, M. Serralha, B.J. Holt, G. Zhang, R. Loh(2), S. Ahlstedt(1), P.D. Sly (1)Karolinska Institute, Sweden, (2)Princess Margaret Hospital, West Perth

A series of studies from our group have established the important principle that asthma is potentially a preventable disease, if appropriate treatments can be instituted in its early stages during which long-term patterns of asthma-associated lung function(s) are "programmed" irreversibly in young children. A crucial requirement for such intervention treatments is development of robust methods for early identification of "at risk" infants and preschoolers who are on the trajectory towards asthma development. Our recent studies have identified two major risk factors for asthma development: expression of the atopic phenotype during the first two years of life as evidenced by production of IgE against aeroallergens, and concomitant lower respiratory tract infections associated with fever or wheeze. Importantly, these risk factors interact quantitatively, and we have devised objective methodology for assessing these interactions. A key finding in this regard is that levels of aeroallergen-specific IgE below the conventional sensitization threshold (0.35kU/L) are associated with asthma risk, if they are present at the time these early infections occur. In principle, armed with information on the number of lower respiratory tract infections accounted during the first two years of life, and aeroallergen-specific serum IgE titres at age two, it is possible to objectively categorise individual children as low versus high asthma risk which in turn determines their suitability as subjects for potential enrolment in asthma prevention trials. We are extending these studies with colleagues in the US who

are collecting similar prospective data on atopy, infections and asthma risk in children, with the long-term aim of developing an internationally applicable diagnostic tool for use in this context.

### TH2-ASSOCIATED IMMUNITY TO MUCOSAL DWELLING BACTERIA IN CHILDREN

E.M. Hollams, B. Hales, C. Bachert(1), W. Huvenne(1), F. Parsons, N.H. de Klerk, M. Serralha, B.J. Holt, S. Ahlstedt(2), W.R. Thomas, P.D. Sly, P.G. Holt. (1)Ghent University Hospital, Belgium; (2)Karolinska Institute, Sweden.

Recent indirect evidence has linked bacterial colonization of the airways with increased risk for childhood asthma. Possibly related to this, IgE against bacterial antigens has been reported in some asthmatics, suggesting a role for bacterial-specific Th2 immunity in disease pathogenesis. We have recently investigated the relationship between IgE against *S. aureus*-specific antigens versus IgE against antigens from *H. influenzae* and *S. pneumoniae* and asthma susceptibility amongst 14-year-olds from the W.A. Pregnancy Cohort. Our findings demonstrate that IgE titres against *S. aureus*-derived superantigens are highest amongst atopics and are associated with risk for asthma, rhinoconjunctivitis and eczema. In contrast, IgE against cell-surface antigens from *H. influenzae* and *S. pneumoniae* is associated with diminished risk, particularly for asthma. We hypothesise that these "protective" IgE responses are a surrogate marker of underlying Th2 immunity in which the key elements are IL-4 and IL-13, which function to suppress activation of phagocytic cells in airway tissues in response to exposure to membrane associated TLR ligands present on the organisms during viral induced asthma exacerbations, resulting from a breakdown of local mucosal barrier functions. Ongoing research is investigating in more detail the relationship between the presence of these different clans of organisms in the upper

airways during early childhood and risk for subsequent asthma development.

This work is funded by the National Health and Medical Research Council of Australia.

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

D. Mok, K. Holt(1), M. Inouye(2), E.M. Hollams, B.J. Holt, M. Kusel, P.D. Sly, P.G. Holt  
(1)Microbiology Department, University of Melbourne; (2) Walter & Eliza Hall Institute, Melbourne

It is well known that viral infections are an important risk factor for asthma development in childhood, but increasing evidence suggests that bacterial infections also play an important role, particularly within the first years of life. We hypothesise that early colonisation of the airways with certain bacterial species predisposes children towards development of asthma, and we are testing this hypothesis in the Childhood Asthma Study (CAS) birth cohort, which comprises children at high-risk for asthma and allergy due to parental history of allergy. Post-nasal aspirate samples have been collected from CAS participants both at regular follow-up appointments and at times of respiratory infection up to age 5 years, and these samples were all cryobanked for future study. We are currently performing a pilot study in collaboration with Dr Kathryn Holt (University of Melbourne) and Dr Michael Inouye (Walter and Eliza Hall Institute), to assess the feasibility of using nasopharyngeal aspirate samples to identify whole bacterial communities within an individual's upper respiratory tract using cutting-edge metagenomics techniques. For this pilot study we have selected 187 post-nasal aspirates obtained from 3-6 month old infants, collected at a routine follow-up without respiratory infection. We extracted DNA from the samples and processed them within our laboratory for bacterial genomic DNA sequencing, which is being performed

at the Ramaciotti Centre at UNSW, using a high-throughput Roche 454 GS FLX Titanium genome sequencer system. Our ultimate aim is to track the changes in bacterial colonisation throughout childhood within the cohort, to examine how this is affected by recurrent respiratory infection, and to determine the relationships between the composition of upper airways bacterial flora and risk for asthma development in childhood.

#### RELATIONSHIPS BETWEEN VITAMIN D STATUS AND ASTHMA AND ALLERGY DEVELOPMENT IN THE W.A. PREGNANCY COHORT ASTHMA AND ALLERGY STUDY.

E.M. Hollams, P. Hart, B.J. Holt, M. Serralha, F. Parsons, N.H. de Klerk, G. Zhang, P.D. Sly, P.G. Holt.

Vitamin D deficiency is now recognised as a world-wide problem, even in Australia. As Vitamin D is needed to regulate the immune system, it has been proposed that a lack of vitamin D could be contributing to the current high rates of asthma and allergy, although this remains controversial. We recently completed laboratory analyses associated with the 14-year follow-up of the W.A. Pregnancy Cohort (WAPC; Raine study), in which we performed extensive clinical and immune profiling on 1380 participants to identify underlying risk factors for asthma and related conditions. We have subsequently measured 25(OH)-vitamin D in plasma collected from cohort members at ages 14 (1380 teens). When we applied the cut-offs most commonly used for determining vitamin D status, at age 14 only 59.3% of the 1380 subjects had what is currently considered sufficient levels of vitamin D ( $\geq 75$  nmol/L); 4.4% were vitamin D deficient ( $< 50$  nmol/L) while 36.3% of subjects had insufficient vitamin D (50-75 nmol/L). Regression analyses showed that low vitamin D at age 14 was a risk factor for current bronchial hyperresponsiveness (BHR) and house dust mite allergy. We then measured vitamin D in plasma collected from 989 WAPC members at age 6 years, when similar respiratory and immunological assessments were undertaken; vitamin D was

measured at both ages for 693 participants. Low vitamin D at age 6 was again associated with increased risk of current BHR and allergy. Further regression analyses showed that low vitamin D at age 6 increased risk of current asthma, rhinoconjunctivitis, BHR and allergic sensitization at age 14. We are in the process of extending these studies into younger age groups, with the particular aim of assessing the impact of partial vitamin D deficiency on early allergic sensitization and respiratory infections during infancy.

This work is funded by the National Health and Medical Research Council of Australia.

#### RISK FACTORS FOR BRONCHIAL HYPERRESPONSIVENESS IN TEENAGERS DIFFER WITH SEX AND ATOPIC STATUS

R.A. Collins, F. Parsons, M. Devereil, E.M. Hollams, P.G. Holt, P.D. Sly.

Bronchial hyperresponsiveness (BHR) is considered to be a cardinal feature of asthma but the overlap is less than perfect, especially in children. Recent data suggest that, rather than being a direct marker of asthma, BHR may in fact be a parallel pathologic process, an idea supported by recent data that suggest separate inheritance of asthma and BHR. We examined members of the W.A. Pregnancy Cohort (WAPC; Raine study) to examine risk factors (in particular from early life) for BHR at age 14, and to determine whether early life risk factors for BHR in adolescence differ between boys and girls. Independent factors that increased risk of BHR at age 14 included female gender, current atopy and current asthma, whereas better lung function (FEF<sub>25-75</sub>/FVC) was protective. Risk factors differed between boys and girls and between atopic and non-atopic children, and current asthma was not a risk for BHR in non-atopic children. Early life factors were generally not independent risk factors for BHR at 14 years of age, with the exception of being smaller at birth for boys only, and maternal asthma for girls only. The results of the present study suggest that genetic predisposition to BHR may be

modulated by sex. Our data also support the close relationship between atopy and BHR in both asthmatic and non-asthmatic subgroups.

This work is funded by the National Health and Medical Research Council of Australia.

## MICROARRAY IDENTIFIES AN IMPORTANT ROLE FOR CD8 T CELLS IN ASTHMA

K.L. McKenna, A. Bosco, P.D. Sly, P.G. Holt

Atopy and polarization of the airway T cell response towards a Th2 phenotype are important factors in the pathogenesis of asthma. However, not all atopic individuals develop asthma. Furthermore, despite allergic disease being typically associated with CD4 T-helper cells, there is growing evidence that CD8 memory T cells may also contribute to disease. In order to elucidate the mechanisms driving the allergen-specific T memory response leading to the development of asthma, we have applied microarray gene expression profiling to identify novel genes and pathways in atopics with or without asthma in allergen-stimulated CD4 and CD8 T cells. Analysis of the CD4 response revealed a small number of genes differentially expressed in asthmatics compared to the non-asthmatic subjects, and many of these genes appear to be part of the Th2 effector cascade. In contrast, there was a much larger response from the CD8 compartment from the same asthmatic subjects. We employed gene coexpression network analysis to the CD8 data and found that most of these differentially expressed genes appear to be highly correlated and hence likely to be coordinately regulated. Bioinformatics tools revealed that these genes are involved in several biological pathways important in development, cell differentiation and wound healing/tissue repair. Ongoing studies will validate the expression of these genes in CD8 T cells, and determine their potential role in airway inflammation employing a co-culture model using airway epithelial cells.

## Pediatric Vaccine Studies

### IMMUNE ONTOGENY IN INFANTS IN THE DEVELOPING AND DEVELOPED WORLD

A.H.J. van den Biggelaar, J. Lisciandro, D.H. Strickland and P.G. Holt in collaboration with S.L. Prescott and P. Richmond (UWA School of Paediatrics and Child Health), and W. Pomat (Papua New Guinea Institute of Medical Research).

The kinetics of maturation of the developing immune system in early infancy impacts upon vaccine responses and is a key determinant of risk for communicable and non-communicable diseases in later life. Accumulating evidence suggests that the functional state of the immune system at birth is predictive of immune maturation processes in infancy. Recently it has been shown that events occurring in utero, such as maternal exposure to distinct environmental cues, can influence the developing immune system. This study aims to identify major differences in neonatal immune function between children born in diverse environmental settings, specifically a low (Papua New Guinea, PNG) compared to high-income setting (Australia, AUS) as a “net outcome of multiple risk factors”. Our initial findings demonstrated that using an autologous culture system, cord blood mononuclear cells (CBMC) from PNG infants display reduced capacity to proliferate compared to the same cells from AUS infants. Our studies then progressed to investigating the functional capacity of major individual cell population(s) within CMBCs, to identify potential mechanisms underlying this reduced proliferation. While PNG and AUS cord naïve T cells (CD4+CD25-CD127+) were found to have similar functional capacity in vitro, including production of cytokines following activation, PNG infants have elevated total numbers of CD4+ T cells in CBMC, potentially enabling a comparatively enhanced T cell response in vivo. In contrast to elevated numbers of CD4+ T cells, PNG CBMC contained lower frequencies of antigen presenting cells (APC). APC from PNG and AUS CBMC were also found to be functionally different, and this difference was the cause for the reduced proliferative

responses of naïve CD4+ T cells in PNG samples. Furthermore, this was linked to reduced capacity of PNG APC to endocytose antigen.

This research was funded by a National Health and Medical Research Council of Australia project grant.

### IMMUNISATION WITH THE DIPHTHERIA TETANUS ACELLULAR PERTUSSIS VACCINE STIMULATES A BALANCED TH1:TH2 MEMORY RESPONSE

O. White, K.L. McKenna, E.M. Hollams, A. Bosco, P.G. Holt in collaboration with P. Richmond, School of Pediatrics and Child Health, UWA and P. McIntyre, National Centre for Immunization Research and Surveillance, Sydney.

Previous studies in our laboratory demonstrated a strongly Th2 polarized memory response to vaccine antigens following immunisation with the diphtheria tetanus acellular pertussis vaccine (DTaP) given at 2, 4, 6 and 18 months, and moreover showed that this Th2 response which displayed an “allergy-like” pattern of cytokine production, was associated with injection site inflammation in some children. We then sought to determine how this vaccine-induced memory response “matured” over time, and to this end set out to further characterize the response following administration of the pre-school DTaP booster at age 4-5 years. We utilized microarray gene expression profiling, and compared the genome-wide vaccine response to the typical allergen-specific memory response elicited by atopic children which also shows a Th2 pattern of cytokine production. Microarray analysis confirmed the expression of Th2 cytokines in response to DTaP vaccine antigens at age 4-5 years. To gain further insight, we employed gene co-expression network analysis, a systems biology approach for modeling and deciphering biological information based on correlation patterns among genes. An underlying principle of network analysis is that gene networks are organized into sets of coordinately regulated genes, known as modules, which may correspond to biological

pathways. In both the vaccine and atopy responses, network analysis identified a module of coordinately regulated genes comprising Th2 signature genes, plus many genes recently identified by our group as important in the Th2 signaling cascade. Furthermore, many of the hyperconnected “hub” genes within each respective module were highly conserved and included the receptors for IL2 and IL4. However, the vaccine-associated network contained an additional module of coordinately upregulated genes that was absent in the atopy network. Bioinformatics tools and pathway analysis revealed this vaccine-associated module to be important in Th1 differentiation, and included genes such as IFNG, IL12, IL12R, STAT1 and IRF1. These genes are key elements in the host defense cellular immune response against bacterial and viral pathogens. These results suggest that vaccination with DTaP results in a mixed Th1/Th2 memory response to vaccine antigens, in which the Th2-associated network supplies essential molecular signals such as IL-4/IL-13 to drive antibody production, in conjunction with a Th1-associated network involving genes which are central to the effector mechanisms underlying sterilizing immunity.

## Animal Model Studies

### PULMONARY IMMUNE RESPONSE AND LUNG FUNCTION ALTERATION IN THE DEVELOPING LUNG SYSTEM AFTER EXPOSURE TO NANOPARTICLES

K.G. Schuepp, D.H. Strickland, J.A. Thomas, A. Larcombe, G. Zosky, P.G. Holt

Nanoparticles have unique physico-chemical properties that provide promising new possibilities for diverse biomedical applications. Considerable research internationally is currently devoted to exploring these potentials of nanotechnology. Applications being investigated include their use as delivery vehicles for lung-based vaccines for children. In this context it is known that larger particles

such as traffic-related pollutants have the potential to harm children’s health. It is known that ambient air can also contain significant levels of nanoparticles from many sources. However, the research effort into the potential health effects of exposure to nanoparticles, especially in children, has been minimal. We hypothesize that the response of the developing respiratory tract to nanoparticle exposure will significantly differ from adult responses and have initiated a research program in this direction. As a prelude we are obtaining baseline developmental data on the pulmonary immune system of Balb/c mice, focusing on differences in cell populations between neonates and adults. In a second step we have commenced investigations on inflammatory changes in bronchoalveolar lavages, immune cell distribution in respiratory tract tissues, and lung function, in Balb/c mice of different ages. Using bioengineered fluorochrome-labelled particles enables us to assess both inflammatory changes as well as particle tracking using flow cytometry. This will give us initial information about nanoparticle translocation and processing in the developing respiratory tract, and during 2011 we will progress to detailed studies on how nanoparticle exposure influences immune defense mechanisms.

### AIRWAY DENDRITIC CELL FUNCTION DURING INDUCTION OF TOLERANCE TO AEROALLERGENS IN MICE.

V. Fear, J. Burchell, S.P. Lai, M. Wikstrom, P.G. Holt, D.H. Strickland\* and P. Stumbles

Chronic innocuous aeroallergen exposure attenuates CD4+ T cell-mediated airways hyperresponsiveness in mice, however the mechanism(s) remain unclear. We have examined the role of airway mucosal dendritic cell (AMDC) subsets in this process using a multi-OVA aerosol induced tolerance model in sensitized BALB/c mice. Aeroallergen capture by both CD11b<sup>lo</sup> and CD11b<sup>hi</sup> AMDC and the delivery of OVA to airway draining lymph nodes (ADLN) by CD8a<sup>-</sup> migratory DC were decreased in vivo (but not in vitro) when compared to sensitized but

non-tolerant mice. This was functionally significant, as in vivo proliferation of OVA-specific CD4+ T cells was suppressed in ADLN of tolerized mice and could be restored by intranasal transfer of OVA-pulsed and activated exogenous DC, indicating a deficiency in antigen-presentation by endogenous DC arriving from the airway mucosa. Bone-marrow derived DC antigen-presenting function was suppressed in multi-OVA tolerized mice, and allergen availability to airway APC populations was limited following multi-OVA exposure as indicated by reduced OVA and dextran uptake by airway interstitial macrophages, diffusion rather than localization of OVA across the airway mucosal surface as a result of decreased epithelial tight junction integrity. These data indicate that inhalation tolerance limits aeroallergen capture by AMDC subsets through a mechanism of bone marrow suppression of DC precursor function coupled with reduced antigen availability in vivo at the airway mucosa, resulting in limited antigen delivery to lymph nodes and hypo-proliferation of allergen-specific CD4+ T cells.

### PERSISTENCE OF AEROALLERGENS IN DRAINING LYMPH NODES IN THE GENERATION OF CD4 T CELLS WITH LUNG-HOMING CAPACITY

M. Wikstrom, E. Batanero, S. Judd, K. Wiquist, P.G. Holt, P. Stumbles

Inhaled allergens are known for their immediate and ongoing effects in the respiratory tract. In this study we have tracked inhaled OVA for seven days in lungs and draining lymph nodes following inhalation in naïve mice. We found that while it is cleared from the airways, OVA persists in peripheral lung tissue and the draining lymph nodes (DLN). The persistence of OVA led to ongoing antigen presentation in the DLN, but not the lungs, that decreased with time in direct proportion with the frequency of antigen-bearing dendritic cells (DC). There was evidence of functional changes amongst the OVA-bearing DC in the DLN: first, the expression of CD40, CD80, and CD86

were modulated over the course of seven days; and second, the generation of recirculating T cells was a feature of early, but not persistent, OVA presentation. These results indicate that antigen persistence is an important determinant of the capacity of migrating DC to generate lung homing T cells in the DLN.

## DEVELOPMENT OF STANDARDIZED METHODOLOGY FOR THE IDENTIFICATION AND ISOLATION OF RODENT RESPIRATORY TRACT DENDRITIC CELLS

P. Stumbles, D.H. Strickland, M. Wikstrom, J.A. Thomas, C. von Garnier, P.G. Holt.

We were commissioned by the publishers to provide a chapter that brings together the recent advances from our lab and elsewhere, on isolation of dendritic cell populations from respiratory tract tissues (published in: *Methods in Molecular Medicine: Dendritic Cell Protocols* 2nd ed. Naik SH (ed). 2010. Humana Press. Chapter 17). This chapter describes the preparation of respiratory tract tissue from both mice and rats for the isolation of respiratory tract dendritic cells (RTDC). The methods describe in detail the preparation of cells from the respiratory tract tissue of the main conducting airways (representing mucosal populations) and peripheral lung (representing predominantly interstitial populations) in both rodent species. Our research in this area has found that these anatomical sites differ in their composition of antigen presenting cell (APC) types including RTDC, and that phenotypic and functional differences exist in RTDC isolated from these sites. We predominantly use a flow cytometry based approach to identify and sort RTDC as this is the most accurate way of isolating RTDC subsets in an environment where many typical dendritic cell surface markers are shared by other APC populations.

## Staff and Students

### HEAD OF DIVISION

Patrick G Holt PhD FRCPATH DSc FRCPI MD(Hon) FAA  
Deputy Director, Telethon Institute for Child Health Research  
Professor, Centre for Child Health Research, UWA  
Senior Principal Research Fellow, National Health & Medical Research Council of Australia

### RESEARCH STAFF

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Kathy McKenna PhD  
Marie Nadal-Sims BSc  
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Deborah Strickland PhD  
Philip Stumbles PhD  
Lily Subrata  
Jenny Tizard  
Michelle Tourigny PhD  
Anita van den Biggelaar PhD  
Jenny Thomas

### POSTGRADUATE STUDENTS

Olivia White PhD

### VISITING RESEARCH FELLOWS

Dr Karen Schuepp MD, University Children's Hospital, Bern, Switzerland.  
Mr Jean-Francois Lauzon-Joset, University of Quebec.

## Theses passed

Angela Rate

## Awards

Elysia Hollams, Best oral presentation "Wheeze and asthma in childhood" Oral Abstracts Session, 29th Congress of the European Academy of Allergy and Clinical Immunology, June 2010, London UK

## External Committees

### INTERNATIONAL

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.

### NATIONAL

Patrick Holt. National Health & Medical Research Council of Australia Career Development Award Committee.

Philip Stumbles. Member, National Health & Medical Research Council of Australia Training Award Committee.

Philip Stumbles. Australasian Society for Immunology (WA Branch) Student Symposium Committee.

Philip Stumbles. Australian Society for Medical Research, WA Medical Research Week Symposium Committee.

Deborah Strickland. National Health & Medical Council of Australia Training Award Committee.

## Presentations 2010

### PATRICK G. HOLT

Symposium Speaker: Early life respiratory infections and atopic sensitization as predictors of childhood asthma - American Academy of Allergy, Asthma and Immunology Congress, New Orleans.

Symposium Speaker: The peanut story – to withhold or not to withhold - American Academy of Allergy, Asthma and Immunology Congress, New Orleans.

Plenary Speaker: Interactions between atopic and antiviral inflammatory pathways in asthma – operation of a lung:bone marrow axis – World Immune Regulation Meeting IV, Davos.

Plenary Speaker: Acute severe asthma exacerbations – underlying mechanisms – Collegium Internationale Allergologicum Congress, Ischia.

Symposium Speaker: Why do some atopic children develop acute severe asthma? European Academy of Allergy & Clinical Immunology Congress, London.

Workshop Speaker: Superantigens in early and late onset allergy – European Academy of Allergy & Clinical Immunology Congress, London.

Plenary Speaker: Prevention of atopic asthma by targeting infections – Trends in Allergy VII, Munich.

Symposium Speaker: Acute severe asthma – Dendritic Cells “in the eye of the storm” – Festschrift for Professor Peter Gehr, University of Bern.

Symposium Speaker: Infection and the development of allergic disease – Symposium on Specific Allergy, Paris.

Symposium Speaker: Primary and secondary prevention of asthma – Washington Airways Workshop, Washington DC.

Plenary Speaker: Aetiology and pathogenesis of asthma in childhood – progress towards development of preventative strategies – 8th APCAAL Congress, Singapore.

Symposium Speaker: Regulation of T-cell immunity to aeroallergens - 8th APCAAL Congress, Singapore.

Plenary Speaker: Host:Microbial interactions in the induction and expression of atopic asthma – 40th Annual Meeting Australian Society for Immunology, Perth.

Symposium Speaker: The asthmatic airway – has the host's defence gone awry? – Pittsburg International Lung Conference, University of Pittsburg.

Institute of Pathology, Rikshospitalet, Oslo, (Professor Frode Jahnsen): Aetiology and pathogenesis of atopic asthma.

Children's Memorial Hospital, Chicago, (Dr X Wang): Cohort studies on the pathogenesis of allergic diseases – recent developments.

### DEBORAH H. STRICKLAND:

Invited Session Chair, Australian Society for Medical Research, Perth; 2010

Judging Committee, Australian Society for Medical Research, Perth; 2010

Organising Committee, ASI Perth

Invited Plenary Speaker, Australian Society of Immunology, Perth; 2010

Chair, New Investigator Session, Australian Society of Immunology, Perth; 2010

### PHILIP STUMBLES

11th International Congress on Dendritic Cells, Lugano, Switzerland, September; 2010

European Respiratory Society Annual Congress, Barcelona, Spain, September; 2010

Dept. of Respiratory Medicine, Bern University, Bern, Switzerland, November; 2010

### ELYSIA M. HOLLAMS

29th Congress of the European Academy of Allergy and Clinical Immunology, London UK; 2010

## 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 involves epithelial cells, contrasting with cancers 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, the Oncology Total Care Unit at Princess Margaret Hospital (PMH) and our Division at the Institute, both members of the largest study group into these diseases, the US-based Children's Oncology Group (COG), work towards a better understanding of these diseases and cure for patients.

The research program of the Division focuses on childhood leukaemia, brain tumours and a form of undifferentiated carcinoma diagnosed in children. 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 the microarray technology to determine gene expression profiles, and experimental model systems, including our panel of established tumour cell lines. They are ideal tools for testing potential new drugs for the treatment of patients.

## Acute lymphoblastic leukaemia

### INTERACTIONS BETWEEN ACUTE LYMPHOBLASTIC LEUKAEMIA AND BONE MARROW STROMAL CELLS INFLUENCE RESPONSE TO THERAPY

Y Tesfai, J Ford, NG Gottardo and UR Kees, in collaboration with MJ Firth, RA O'Leary and KW Carter, Division of Biostatistics and Genetic Epidemiology, and C Cole, Department of Haematology-Oncology, Princess Margaret Hospital.

The cure rate for paediatric patients with B precursor acute lymphoblastic leukaemia (pre-B ALL) is steadily improving, however relapses do occur despite initial response to therapy. To identify links between drug resistance and gene deregulation we used oligonucleotide microarray technology and determined in 184 pre-B ALL specimens genes differentially expressed compared to normal CD34+ specimens. We identified 20 signature genes including CTGF, BMP-2, CXCR4 and IL7R, documented to regulate interactions in the bone marrow. We recorded remarkably similar levels of expression in three independent patient cohorts, and found distinct patterns in cytogenetically defined subgroups of pre-B ALL. The canonical pathways that were affected are involved in inter- and intra-cellular communication, regulating signaling within the microenvironment. We tested experimentally whether interaction with stromal cells conferred protection to four drugs used in current ALL therapy, and demonstrated that bone marrow stromal cells significantly influenced resistance to vincristine and cytosine arabinoside. Compounds designed to block the identified cellular interactions within the bone marrow microenvironment are expected to mobilise the leukaemic cells and make them more accessible to contemporary antileukaemic agents. The data provide novel insight into the pathobiology of ALL and indicate new therapeutic targets for patients with ALL.

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

### ROLE OF MICROENVIRONMENT INTERACTIONS IN CHILDHOOD LEUKAEMIA

JE Wells, J Ford, AL Samuels 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 origin and proliferation. Recently, bone marrow stromal cells have been revealed to play a critical role in leukaemic cell survival and drug resistance, a major component of clinical outcome. The mechanism by which this stromal protection takes place is unclear. We performed transcriptional profiling of B precursor (pre-B) ALL compared to normal CD34+ cells to identify genes and pathways linked to the disease and drug resistance. 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 (HS5) 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 HS5 cells incubated with CTGF revealed changes to the stromal cell expression profile. This clear link between CTGF and pre-B ALL -microenvironment interactions will be validated and further characterised in vitro through endogenous overexpression of CTGF in pre-B ALL cells using stable lentiviral transfection. We hypothesise that secretion of CTGF initiates a cascade of events, contributing to leukaemogenesis and adhesion-mediated drug resistance. Delineation of 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 the Cancer Council of WA and the Children's Leukaemia and Cancer Research Foundation, WA.

#### CPG ISLAND METHYLATION CORRELATES WITH CTGF GENE EXPRESSION IN PAEDIATRIC PRE-B ACUTE LYMPHOBLASTIC LEUKAEMIA

M Welch and UR Kees in collaboration with WK Greene, Division of Health Science, Murdoch University, Perth.

Acute lymphoblastic leukaemia (ALL) is the most common form of childhood cancer, with precursor B-cell (pre-B ALL) comprising around 80 percent of ALL cases. Using microarray technology we compared the gene expression profile of pre-B ALL to normal CD34+ and CD19+/IgMneg cells. Many of the top ranked genes identified in this study are known to mediate cell-cell interactions. One of them, connective tissue growth factor (CTGF) has been implicated in the biology of several solid tumours. Four independent studies on B-lineage ALL in paediatric and adult patients showed that 75 percent of patients expressed CTGF at very high levels, and in our paediatric patient specimens CTGF was expressed over a wide range from 2.3 to 380-fold by array measurement. Immunoblotting confirmed secretion of CTGF in our panel of pre-B ALL cell lines and interestingly, novel variants of CTGF mRNA were identified in several CTGF-positive cell lines by RNA blotting and sequencing of RACE products. CTGF is not normally expressed in B cells or their progenitors and secretion of CTGF proteins may play a prominent role in ALL, leading to modified interactions with the microenvironment.

The present study focused on investigating the mechanism of CTGF gene deregulation by genetic and epigenetic mechanisms. Analysis of the CTGF locus by Southern blotting ruled out rearrangements disturbing the CTGF locus. A combination of bisulfite sequencing and methylation-specific PCR identified epigenetic regulation of CTGF in our panel of pre-B ALL cell lines. Demethylation of CpG dinucleotides across the CTGF CpG island was a feature of CTGF positive

cell lines, while those lacking CTGF expression were hypermethylated at this locus. The study has now been extended to include primary patient specimens. Future experiments aim to examine the effect of pharmacological modulation of CpG methylation upon CTGF expression in vitro.

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.

#### OUTCOME PREDICTION OF PAEDIATRIC PATIENTS WITH ACUTE T-CELL LYMPHOBLASTIC LEUKAEMIA AT DIAGNOSIS

AL Cleaver, AH Beesley, NC Sturges and UR Kees, in collaboration with MJ Firth and RA O'Leary, Division of Biostatistics and Genetic Epidemiology and DL Baker, Department of Haematology-Oncology, Princess Margaret Hospital, Perth.

Continuous complete clinical remission in T-cell acute lymphoblastic leukaemia (T-ALL) is now approaching 80% due to the implementation of aggressive chemotherapy protocols, but patients that relapse continue to have a poor prognosis. Such patients could benefit from augmented therapy if their clinical outcome could be more accurately predicted at the time of diagnosis. Gene expression profiling offers the potential to identify additional prognostic markers, but has had limited success in generating robust signatures that predict outcome across multiple patient cohorts. This study aimed to identify robust gene classifiers that could be used for the accurate prediction of relapse in independent cohorts and across different experimental platforms. Using HG-U133Plus2 microarrays we modelled a five-gene classifier

(5-GC) that accurately predicted clinical outcome in a cohort of 50 T-ALL patients. The 5-GC was further tested against three independent cohorts of T-ALL patients, using either qRT-PCR or microarray gene expression, and could predict patients with significantly adverse clinical outcome in each. The 5-GC featured the interleukin-7 receptor (IL-7R), low-expression of which was independently predictive of relapse in T-ALL patients. In T-ALL cell lines, low IL-7R expression was correlated with diminished growth response to IL-7 and enhanced glucocorticoid resistance. Analysis of biological pathways identified the NF- $\kappa$ B and WNT pathways, and the cell adhesion receptor family, particularly integrins, as being predictive of relapse. Outcome modelling using genes from these pathways identified patients with significantly worse relapse-free survival in each T-ALL cohort. We have therefore used two different approaches to identify, for the first time, robust gene signatures that can successfully discriminate relapse and continuous complete remission patients at the time of diagnosis across multiple patient cohorts and platforms. Such genes and pathways represent markers for improved patient risk stratification and potential targets for novel T-ALL therapies.

This work was supported by the National Institutes of Health, USA and the Children's Leukaemia and Cancer Research Foundation, WA.

## MODELS OF DRUG-RESISTANCE TO PREDICT PATIENT OUTCOME IN ACUTE LYMPHOBLASTIC LEUKAEMIA

AH Beesley and UR Kees in collaboration with RA O'Leary 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 (CCR) with early response to drug therapy being one of the strongest predictors of outcome. However, a significant number of

patients continue to relapse and for these the outlook is dismal due to the development of drug-resistance. Identifying potential markers of drug-resistance could improve patient stratification and further improve cure rates. Over the past 20 years our laboratory has developed a panel of paediatric ALL cell lines that retain critical features of the primary disease. Using the MTT viability assay we have measured the sensitivity of these cell lines to 13 commonly used ALL chemotherapeutic agents and have measured gene-expression profiles by Affymetrix HG-U133A microarray. In contrast to many of the cell lines that are available commercially, our cell lines generally grow at slow rates similar to the growth of leukaemic blasts in vivo. Their drug-resistance profile parallels the spectrum of resistance that has been observed in primary patient specimens, particularly in regard to dexamethasone. We have correlated drug-resistance and gene-expression profiles to generate an extensive database of drug-gene signatures that are currently being analysed for biological function. Comparison of drug-gene signatures with the publicly available Connectivity Map has provided potential drug-leads that are under test in our laboratory. We are also in the process of developing a gene expression-algorithm based on our in vitro drug-gene resistance data that can predict outcome in primary patient specimens. The data was used to generate a model of predicted resistance scores that was subsequently assessed in microarray datasets from three independent T-cell ALL (T-ALL) patient cohorts. These scores were used to predict patient outcome (relapse or CCR) in each cohort. The top 50 genes correlating with in vitro resistance to each of the ten drugs were used in modelling. Using this model, relapse/CCR patient status could be predicted with  $\rightarrow$ 75% accuracy in each of the three independent cohorts. Predictions of relapse were driven by contributions from different drug combinations in each of the cohorts, indicating particular importance in T-ALL therapy. These findings demonstrate that biological pathways correlating to in vitro drug resistance may have prognostic potential in patients and highlight the importance of understanding how individual

patients relapse. These genetic features contribute to our understanding of drug resistance and represent potential markers for improved patient stratification at diagnosis.

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

## ALTERED GLUCOSE METABOLISM IN DRUG-RESISTANT PAEDIATRIC T-LINEAGE ACUTE LYMPHOBLASTIC LEUKAEMIA

AL Samuels, J Heng, UR Kees and AH Beesley.

Despite significant improvements in the treatment of T-cell acute lymphoblastic leukaemia (T-ALL), as many as 30% of paediatric and 50-70% of adult patients develop treatment-resistant disease, which carries 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. Using a panel of paediatric GC-resistant cell lines we recently demonstrated altered expression of genes associated with glucose metabolism. 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. In addition, we have developed a novel metabolomic profiling approach using gas chromatography mass spectrometry to investigate the global metabolic alterations that occur in drug-resistant leukaemia. Our in vitro cell line data suggests that GC-resistance is associated with an increased glycolytic phenotype and protection for metabolic crisis in T-ALL. Preliminary metabolomic analysis also indicates that significant changes at the metabolic level are associated with drug resistance. 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 bioenergetic mechanisms underlying drug resistance in leukaemia is critical and may identify novel drug targets. Incorporation of selective metabolic inhibitors into current treatment regimens may improve treatment for drug-resistant leukaemia.

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

#### **METABOLIC AND PROTEOMIC ANALYSIS OF GLUCOCORTICOID RESISTANCE IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA (T-ALL)**

AL Samuels, AH Beesley and UR Kees in collaboration with RW Francis and KW Carter, Division of Biostatistics and Genetic Epidemiology.

Despite significant improvements in the treatment of childhood T-ALL, as many as 20% of patients will relapse and most of those face a dismal prognosis. Resistance to glucocorticoids 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. Recent studies in our laboratory identified that leukaemia cells resistant to glucocorticoids alter their central metabolism and enhance glucose catabolism. The aim of this study is to interrogate the leukaemia metabolome and proteome to identify metabolites and proteins associated with glucocorticoid resistance, conducted in collaboration with Metabolomics Australia and Proteomics International. Using this novel profiling approach will allow us to identify key cellular changes that occur in glucocorticoid-resistant cells compared to sensitive cells. 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 is supported by the Cancer Council of WA.

#### **INFLUENCE OF WILD-TYPE MLL ON GLUCOCORTICOID SENSITIVITY AND RESPONSE TO DNA-DAMAGE IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA**

AH Beesley, JL Rampellini, ML Palmer, JYS Heng, and UR Kees, in collaboration with MJ Firth, Division of Biostatistics and Genetic Epidemiology.

Rearrangement of the mixed-lineage leukaemia gene (MLL) is found in 80% of infant acute lymphoblastic leukaemia (ALL) and is associated with poor prognosis and resistance to glucocorticoids (GCs). We have recently observed that GC resistance in T-cell ALL (T-ALL) cell lines is associated with a proliferative metabolism and reduced expression of MLL. In this study we further explored the relationship between MLL status and GC sensitivity. Negative correlation of MLL expression with GC resistance in 15 T-ALL cell lines was confirmed by quantitative RT-PCR. The absence of MLL rearrangements suggested that this relationship represented expression of wild-type MLL. Analysis of MLL expression patterns revealed a negative relationship with cellular metabolism, proliferation and anti-apoptotic transcriptional networks. In silico analysis of published data demonstrated that reduced levels of MLL mRNA are associated with relapse and prednisolone resistance in T-ALL patients and adverse clinical outcome in children with MLL-rearranged ALL. RNAi knockdown of MLL expression in T-ALL cell lines significantly increased resistance to dexamethasone and gamma irradiation, indicating an important role for wild-type MLL in the control of cellular apoptosis. The data suggests that reduced expression of wild-type MLL can contribute to GC resistance in ALL patients both with and without MLL translocations.

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

#### **CORRELATION OF NOTCH1 ACTIVATING MUTATIONS AND SENSITIVITY TO 6-MERCAPTOPYRINE IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA CELL LINES**

AD Schoof, AH Beesley, NG Gottardo and UR Kees in collaboration with JD Jago, Curtin University of Technology, Perth.

Acute lymphoblastic leukaemia (ALL) is the most common cancer in children, with T-cell ALL (T-ALL) occurring in about 15% of cases. Using the current Children's Oncology Group protocol 5-year event free survival rates approaching 80% can be achieved. However, for the patients that relapse many become resistant to the current chemotherapeutic drugs and a cure remains hard to achieve. NOTCH1, a critical developmental gene, was implicated in T-cell leukaemogenesis by the discovery of a t(7;9) translocation. More recently, activating mutations of NOTCH1 have been demonstrated in over 50% of T-ALL patient specimens. Based on these observations we wished to (i) determine the mutational status of NOTCH1 in our unique panel of T-ALL cell lines and (ii) to correlate the presence of NOTCH1 activating mutations with the drug resistance profiles for these cells. DNA was extracted from 12 cell lines and NOTCH1 exons were PCR amplified and sequenced. Activating mutations of the NOTCH1 gene were identified in 7 of the panel of 12 cell lines (58%). One cell line had a mutation in the juxtamembrane domain, three cell lines had a mutation in the heterodimerization domain only, and one cell line had a mutation in the PEST domain, whilst two cell lines had mutations in both the heterodimerization and PEST domains. The drug resistance profile of the T-ALL cell line panel for standard chemotherapeutic agents used in the clinic to treat T-ALL (including cytosine arabinoside, 6-mercaptopurine, 6-thioguanine, methotrexate, dexamethasone, methylprednisolone, daunorubicin, doxorubicin, L-asparaginase and vincristine) were then correlated to NOTCH1 mutation status. This revealed that cell lines with NOTCH1 activating mutations were more susceptible to

6-mercaptopurine and 6-thioguanine than cell lines without NOTCH1 activating mutations, indicating that they may be more important in T-ALL therapy than has been previously appreciated. We are currently expanding this research to include additional T-ALL cell lines and to study mutations in the FBW7, PTEN, P53, and TPMT genes, which have relevance either for NOTCH1 signalling or thiopurine sensitivity. Such studies have important implications for improved risk stratification and the development of individualised treatment strategies.

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

## NOVEL DRUG THERAPY COMBINATIONS FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

AH Beesley, E Ferrari, J Ford, and UR Kees.

The hallmark of therapy for paediatric patients with acute lymphoblastic leukaemia (ALL) is the use of multiple drugs to avoid the development of resistance. Optimal therapy for patients with ALL should comprise drugs that effectively complement each other with respect to their mechanism of action and have a minimal effect on normal cells. Ultimately a paradigm shift is required to arrive at a combination of drugs that is necessary and sufficient to cure ALL patients, and such drug combinations may in the future be tailored to each patient. The current multi-agent protocols are very successful and they invariably include steroid drugs, which induce apoptosis in lymphoid malignancies but not in others. Despite their major impact on clinical outcome, studies of relapsed ALL have clearly demonstrated that resistance to steroids is the most prominent feature compared to all other drugs and new ways to tackle this problem are required. Importantly, our recent studies in ALL cell lines have revealed that the novel agent flavopiridol (FP) is highly effective in steroid-resistant cells. FP when administered in a pharmacologically-derived schedule in adults and children has

been shown to achieve marked clinical efficacy in refractory haematopoietic malignancies, including acute leukaemias and relapsed high-risk chronic lymphoblastic leukaemia (CLL). Liposomes containing FP have recently been produced and this formulation has achieved significantly improved pharmacokinetics. However, the evidence that development of steroid resistance in ALL contributes to relapse makes it highly likely that clinical resistance to FP would also ultimately evolve, as has been the case for the drug Gleevec. The objectives of this on-going study are to study the biological actions of FP and to derive FP-resistant ALL cell lines with which to investigate potential mechanisms of FP-resistance before the phenomenon is known in the clinic. This knowledge will contribute to the application of this novel therapy to the treatment of drug-resistant ALL.

This work is supported by 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-EPS15/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 EPS15 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 is supported by the Children's Leukaemia and Cancer Research Foundation, WA, and the Whiteman Fellowship.

## INTERROGATING DRUG RESISTANCE USING A XENOGRAFT MODEL OF LEUKAEMIA RELAPSE

AL Samuels, VK Peeva, AH Beesley and UR Kees in collaboration with RA Papa and RB Lock, Children's Cancer Institute Australia, Sydney, Australia.

Despite significant improvements in the treatment of childhood T-cell acute lymphoblastic leukaemia (T-ALL), up to 30% of patients relapse with most facing a dismal prognosis. Drug resistance continues to be a significant problem in 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 clones *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 expression profiles among the *in vivo* drug-selected T-ALL xenografts and controls, which revealed up-regulation of genes encoding oncogenes and nutrient metabolism regulators. 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-methylglutaryl Coenzyme A reductase (HMG-CoA). We are currently testing *in vitro* the efficacy of these molecules, both as single agents and in combination, using a unique drug-resistant cell line panel, as well as in the xenograft leukaemia relapse model. Ultimately, this study will allow us to answer fundamental questions regarding molecular pathways deregulated by the development of drug resistance *in vivo*, and contribute to the identification of novel therapeutics for relapsed ALL.

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

#### THE ROLE OF CLASS 1A ALDEHYDE DEHYDROGENASE (ALDH1A) RETINOIC ACID-SYNTHESIZING ENZYMES IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA (T-ALL)

BAC Longville, J Ford, AH Beesley and UR Kees, in collaboration with WK Greene, School of Veterinary and Biomedical Sciences, Murdoch University, Perth.

Several T-ALL oncogenes are known, of which TLX1/HOX11 and SCL/TAL1 are deregulated in over 50% of T-ALLs. These genes encode transcription factors and are thought to represent critical first-hit events, resulting in the emergence of pre-leukaemic T-cells with altered self-renewal and/or survival capabilities. ALDH1A genes, which encode enzymes responsible for retinoic acid (RA) synthesis, have been identified as being downstream of both TLX1 and SCL and are frequently expressed in T-ALL, but not in normal thymocytes. Enforced expression of an ALDH1A gene can perturb both T-cell differentiation and haematopoiesis in general. Moreover, it has been well documented that RA is stimulatory to T-cell growth and survival. We therefore hypothesise that aberrant synthesis of RA may play a crucial role in the pre-leukaemic immortalization of thymocytes and/or maintenance of the T-ALL phenotype, the latter being the more immediate focus.

The aim of this study was to determine whether it is possible to inhibit T-ALL proliferation by experimentally modulating the RA pathway, and to discover the most effective method for doing so. We examined the effects of citral, a retinoic acid inhibitor, TTNPB, a pan-RAR (retinoic acid receptor) agonist, and Ro-415253, a RAR-alpha antagonist, and cell survival was measured using the MTT viability assay. Four human T-ALL cell lines and two human B-cell ALL (B-ALL) cell lines were investigated. These experiments were designed to elucidate potential differences in the synthesis and importance of RA in T-ALL compared with B-ALL. Our results to date demonstrate a heightened citral sensitivity ( $p = 0.0003$ ) in T-ALL cell lines versus B-ALL cell lines, lending support to our hypothesis.

Analysis of gene expression microarray data of 100 primary specimens from T-ALL patients versus 2 normal thymocytes was conducted to determine biologically plausible downstream targets of the RA pathway. Real-time quantitative RT-PCR is currently being utilised to study differential expression of the ALDH1A and six candidate genes in the panel of cell lines in the presence and absence of RA inhibition.

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

## Carcinomas

#### NOVEL BRD4 TRANSLOCATION IN UNDIFFERENTIATED CARCINOMA

K Thompson, AH Beesley and UR Kees, in collaboration with E Baker and A Murch, King Edward Memorial Hospital for Women, Perth, and AK Charles and M Phillipps, Princess Margaret Hospital, Perth.

Four years ago a 16-year old female patient was diagnosed at Princess Margaret Hospital (PMH) with a poorly differentiated lung carcinoma which had the hallmarks of a rare but almost invariably fatal carcinoma arising in the midline organs, known as a NUT midline carcinoma. These cancers are characterised by translocations between chromosome 15 and 19 and in most cases the breakpoint on chromosome 19 contains the BRD4 bromodomain gene and the NUT gene on chromosome 15. This translocation was present in the cell line PER-403 established from an 11-year old girl diagnosed at PMH several years ago. The 16-year old patient received combination chemotherapy at PMH and she initially responded well, however died from disease 8 months after diagnosis. We generated cell line PER-624 from her cancer cells and have determined that they contain several karyotypic abnormalities, including t(6;19) and t(1;18;7) but not the standard translocation. FISH experiments were performed using whole chromosome paints, BACs, subtelomere and PCR probes to determine the nature of these

karyotypic abnormalities. These studies have shown that in this case BRD4 and a region of 19p were cryptically inserted into chromosome 15, co-localising next to the NUT gene. To further characterise this carcinoma we used RNA sequencing to investigate the transcriptome. We identified that there is a BRD4-NUT fusion gene in the PER-624 cells but that it has a novel breakpoint which is different to the standard NUT-midline carcinomas. We have confirmed this breakpoint using RT-PCR. This novel fusion breakpoint, coupled with the FISH data suggests that there is alternative splicing occurring at the RNA level. We are currently undertaking genomic sequencing of the PER-403 and PER-624 cell lines to identify the exact nature of the genomic breakpoints in these cells. We also conducted a review of patient data from PMH and have identified another NMC case and two other carcinoma cases of interest. We have developed cell lines from these patient specimens and are planning to do further transcriptome sequencing on these carcinomas. This sequencing will enable us to identify the fusion genes present, as well as a comparison of the gene expression profiles of the NMCs.

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

## Paediatric Brain Tumours

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

CM Bertram, DJ Holthouse, L Genovesi, PI Fuller, UR Kees, 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 chromosomal aberrations in a panel of paediatric brain tumour cell lines using cytogenetic analysis, representational difference analysis, and microsatellite mapping. To further refine our focus to specific regions of the human genome, we have correlated our extensive cytogenetic data with the gene expression profiles of our panel of brain tumour 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.

Several genes, including the zinc finger transcription factor ZIC1 and the putative oncogene MINA53 were significantly

up regulated in MB compared to all control cell types. The functional significance of deregulated expression of these and other genes identified using this approach is being explored using virus-mediated manipulation of gene expression in NSCs. This system is expected to provide new insight into the link between deregulated NSC growth and MB pathogenesis, which will ultimately facilitate the design of more effective drugs and treatment

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

### THE ROLE OF FOXO1A IN MEDULLOBLASTOMA PATHOGENESIS

PB Dallas, L Genovesi, and UR Kees.

A comprehensive molecular analysis of our panel of primary MB and MB cell lines identified a tumour suppressor gene, FOXO1A, which was significantly down regulated in the majority of tumour specimens. Importantly, this gene functions in pathways that regulate critical aspects of stem cell growth and differentiation. We are assessing the roles of FOXO1A in the regulation of proliferation and differentiation of normal human neural stem cells (NSCs), a cell type from which some MB are thought to arise. The manipulation of target gene expression levels in MB cell lines and NSCs is being undertaken using adenovirus-based over-expression or RNAi knockdown procedures. Reconstitution of FOXO1A expression in FOXO1A null cell lines does not reduce proliferation or induce apoptosis either under normal growth conditions or in response to chemotherapeutic agents. Consistent with these data, FOXO1A knockdown in NSCs does not affect proliferation. These results suggest that the down-regulation of FOXO1A generally observed in MB may be linked to deregulated self-renewal or differentiation pathways during brain tumour development. We are currently investigating these possibilities. A detailed understanding of the role of FOXO1A in MB pathogenesis may provide important new clues about molecular approaches to treatment that target FOXO1A-

regulated biochemical pathways.

This work was supported by the NHMRC, Australia and John Lillie Fellowship (PBD).

#### THE CHARACTERISATION OF DEREGULATED MICRORNA EXPRESSION IN PAEDIATRIC BRAIN TUMOURS

L Genovesi, K Carter and PB Dallas in collaboration with KM Giles, 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. We are currently investigating this possibility. 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 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 John Lillie Fellowship (PBD).

#### DEVELOPMENT OF A MOUSE EPENDYMOMA MODEL

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 signalling 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 Blbp promoter and concurrently deleting 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 Fellowship (NGG).

#### TESTING NOVEL THERAPIES IN CHILDHOOD BRAIN TUMOUR MODELS

CL Burchill, PB Dallas, and NG Gottardo.

Medulloblastoma, pineoblastoma and ependymoma constitute the most common malignant brain tumours of childhood. Many children with these tumours remain incurable and survivors are often left with devastating long-term side effects. Whilst many novel targeted anti-cancer agents have been developed, to date only a small number have revealed clinical efficacy. One reason is due to the lack of model systems that accurately reflect the disease in children. To address this issue, we have previously generated a panel of unique cell lines, which have been cultured in the absence of drug selection, representative of the various medulloblastoma subtypes and pineoblastoma. In addition, to more closely resemble the tumours natural microenvironment, we have established an orthotopic xenograft mouse model system representative of the various medulloblastoma subtypes and pineoblastoma. We have also acquired a transgenic spontaneous mouse model of medulloblastoma, the Smoothed (Smo) mouse, which develops spontaneous medulloblastoma due to the over-expression of the sonic-hedgehog pathway component Smo. We hypothesise that the use of these models will accelerate the investigation of combined conventional agents with targeted agents in clinical trials. Using the MTT cell proliferation assay we have determined the drug sensitivity profiles for our panel of brain tumour cell lines to conventional anti-cancer therapies currently used in the clinic for these tumours, including vincristine, cyclophosphamide, cisplatin, lomustine (CCNU) and temozolomide. These profiles will form the basis for combinatorial studies using novel therapies. In addition, to uncover novel genes and biological pathways involved in the development of resistance to these drugs, we are also correlating the drug sensitivity profiles with the gene expression profiles.

We are currently assessing two novel compounds, alone and in combination with the chemotherapeutics above. The first

compound, PF-00299804, developed by Pfizer, irreversibly targets the ERBB signalling pathway, which has been shown to be over-expressed in the majority of medulloblastomas and ependymomas. The second compound, CDDO-IM, a synthetic triterpenoid has shown anti-tumorigenic activity in many cancer types and been demonstrated to inhibit the anti-apoptotic protein CFLAR/FLIP. We found CFLAR/FLIP was significantly up-regulated in medulloblastoma samples relative to their putative normal cellular counterpart, implicating this gene in the development of medulloblastoma. We speculate that up-regulation of CFLAR in MB may be responsible for resistance to cytotoxic agents and that inhibition of CFLAR may sensitise cells to apoptosis. The best combinations, as determined from in vitro experiments, will then be assessed in our mouse model systems.

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

## PAEDIATRIC MENINGIOMA: CURRENT APPROACHES AND FUTURE DIRECTIONS.

RS Kotecha, UR Kees, AH Beesley, NG Gottardo, in collaboration with RC Junckerstorff, Royal Perth Hospital, Perth and S Lee and CH Cole, Princess Margaret Hospital for Children, Perth.

With improvement in leukaemia therapy, central nervous system (CNS) tumors are the leading cause of cancer mortality in children and the most expensive of all human neoplasms to treat. Meningiomas are rare intracranial tumors in childhood and adolescence, arising from arachnoid cell clonal outgrowth in the meninges. There have been no collaborative prospective therapeutic trials for paediatric meningioma because of its rarity, and the best evidence for management comes from retrospective case analyses and extrapolation from the treatment of adult meningioma. However this may not be ideal, because the underlying biology of adult and

paediatric meningiomas seems to be different, as is the case for other CNS tumors. In addition, treatment of paediatric brain tumors requires consideration of long-term quality of life. We are currently conducting a meta-analysis to review what is currently known about the treatment of paediatric meningioma globally, and identify opportunities for future directions. We are also actively recruiting primary specimens to begin ground-breaking molecular analysis of the genetic defects driving this rare disease.

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

## Staff and Students

### HEAD OF DIVISION

Ursula R Kees PhD

Adjunct Professor University of Western Australia  
Consultant, Department Haematology/Oncology, Princess Margaret Hospital for Children

### RESEARCH STAFF

Alex H Beesley, PhD, Adjunct Senior Lecturer UWA  
Peter B Dallas, PhD, Adjunct Senior Lecturer UWA, John Lillie Fellow

Nicholas Gottardo, MB ChB FRACP (Paeds.) PhD, Adjunct Senior Lecturer UWA, John Lillie Fellow

Wayne K Greene, PhD, Senior Lecturer Murdoch University

Jette Ford, BApplSc, Grad Dip Comp

Amy Samuels, PhD, BSc (Hons)

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Jasmin YS Heng, BSc (Hons)

Brooke Longville, PhD, BSc (Hons)

Chantel Burchill, BSc (Hons)

Paula Fuller, BSc (Hons)

Emmanuela Ferrari, BSc (Hons)

### POSTGRADUATE STUDENTS

Misty-Lee Palmer, BSc (Hons), PhD candidate

Cornelia Bertram, MBs, PhD candidate

Mathew Welch, BSc (Hons), PhD candidate

Laura Genovesi, BSc (Hons), PhD candidate

Laurence Cheung, BSc (Hons), PhD candidate

Julia Wells, BSc (Hons), PhD candidate

Rishi Kotechi, MB ChB, PhD candidate

Ashley Schoof, BSc (Hons), PhD candidate

## RESEARCH SUPPORT

Stewart Cattach

## ADMINISTRATIVE SUPPORT

Joanne Graham

## External Committees

### INTERNATIONAL

Ursula Kees. COG-B969, Children's Oncology Group, USA Chair (2000-)

### NATIONAL

Peter Dallas. Australasian Society for Stem Cell Research, Conference Organising Committee.

Peter Dallas. Australian Children's Clinical Trials Group.

Nicholas Gottardo. Australian Children's Clinical Trials Group

Nicholas Gottardo. The Cure Starts Now Foundation Medical Advisory Committee

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

### REGIONAL

Ursula Kees. Cancer Council of Western Australia

Ursula Kees. Research Advisory Committee, School of Pathology and Laboratory Medicine, UWA and PathWest.

Amy Samuels. Australian Society for Medical Research Committee, deputy co-convenor (2009-).

Amy Samuels. Chair ASMR networking committee (2009-)

Amy Samuels. UWA Post-doctoral consultation group (2009-)

Amy Samuels. UWA Post-Doctoral Advisory Committee (2009-)

Katherine Thompson. Australian Society for Medical Research Committee, deputy co-convenor (2009-).

## Invited Presentations

Ursula Kees: AACB/AIMS Combined Scientific Meeting, Perth. October 2010. "Personalised therapy in children's acute lymphoblastic leukaemia: the goal and the reality".

Ursula Kees: ARRAY Day, Perth. November 2010 "Array studies on paediatric cancers and xenograft models".

Peter Dallas: The molecular pathogenesis of medulloblastoma. UWA School of Pathology and Laboratory Medicine Seminar Series. Royal Perth Hospital, WA, Nov, 2010.

Peter Dallas: Cancer stem cells and brain tumours. Science Teachers of Western Australia. Future Science Workshop. Murdoch University WA, Dec 2010.

Nick Gottardo: Paediatric Brain Tumours. Royal Australasian College of Physicians Annual Scientific Meeting. Melbourne, March 2010.

## Funding awarded in 2010

Children's Leukaemia and Cancer Research Foundation (CLCRF) Grant (2009 - 2012): 'Therapy for steroid-resistant paediatric acute lymphoblastic leukaemia' (Kees UR, \$1,247,671 over 3 years).

NHMRC Project Grant 513765 (2008 - 2010): 'A Pre-Clinical Model of Relapse in Acute Lymphoblastic Leukaemia' (Kees UR, Lock RB, Beesley AH, \$551,000 over 3 years).

Cancer Council WA Project Grant (2009 - 2010): "The role of retinoic acid-synthesising enzymes aldehyde dehydrogenase

(ALDH) 1A1 and 1A2 in T-cell acute lymphoblastic leukaemia" (WK Greene and UR Kees, \$140,000 over 2 years).

John Lillie Research Fellowship 2009-2012; jointly awarded to Dr Peter Dallas and Dr Nicholas Gottardo for brain tumour research.

Cancer Council WA Early Career Investigator Grant, "Metabolic analysis of glucocorticoid resistance in T-cell acute lymphoblastic leukaemia", (A Samuels, \$25,000).

Cancer Council WA Early Career Investigator Grant, 'Transcriptome sequencing to detect novel fusion genes in a rare, aggressive carcinoma' (K Thompson, \$23,408).

Children's Leukaemia and Cancer Research Foundation (CLCRF) Travel Grant (April, 2010): (K Thompson, \$6,345) 2010 American Association for Cancer Research Conference and visit to collaborating researchers, Boston, Mass. USA.

Cancer Council WA Grant (2010 - 2011) "Microenvironmental interactions in acute lymphoblastic leukaemia mediated by connective tissue growth factor" (UR Kees, \$140,000 over two years)

The University of Western Australia Research Development Award, (A Samuels, \$27,500).

Apache Energy Research Fellowship in Children's Cancer (2010 - 2012. \$300,000)

PMH Foundation Translational Research Grant. 'Targeting apoptosis pathways in medulloblastoma'. (NG Gottardo and PB Dallas. \$48,401)

Pfizer Investigator initiated grant. 'A preclinical study of the effects of the pan-Her inhibitor PF-00299804 (PF) on the growth of brain tumour cells'. (NG Gottardo, PB Dallas, DM Ashley, TG Johns. \$60,400)

## Overview

The Drug Discovery Technology Unit has made significant progress on a number of fronts.

i) In August 2010 a discovery contract was signed between Phylogica and Medimmune, the biologics arm of AstraZeneca to discover new antimicrobials against *Pseudomonas aeruginosa* an important cause of hospital acquired multi-resistant infections.

iii) In December 2010, we signed another third discovery contract with Pfizer vaccines

v) Our collaboration with Cambridge University to conduct phenotypic screens using our Phylomer peptide libraries to discover new targets was so successful that a joint spin-off between Phylogica and Cambridge University has been created. This is called 'Phenomica' and will be focussed on target discovery and validation using Phylomer peptides.

### IMPROVING PHYLOMER® LIBRARIES AND SCREENING PROCESSES

Phylogica's current libraries are the most structurally diverse biologics discovery libraries available with billions of compounds from thousands of distinct structural families. This vast diversity of molecular shapes means more hits can be obtained against a wider variety of targets. Ongoing efforts are focused on refining existing libraries and expanding our repertoire of phylomer libraries (8 new libraries were constructed in 2009 and several more have been constructed in 2010 and 2011). Some of these libraries are customised for the company's contracted commercial projects, for example the new collaboration with Pfizer.

### DISCOVERING NEW CELL PENETRATING PEPTIDES (COLLABORATION WITH ROCHE)

Phylogica has a contract with Roche, Europe's largest pharmaceutical company). Roche is now the largest company in the 'biologics' (large molecule drugs) space and has a track record in cutting edge peptide drug discovery.

The Drug Discovery Technology Unit is now working with Roche's biologics R&D team using Phylomer peptides as intracellular targeting agents, to enhance our opportunities for discovery of a number of different drugs by transporting them into cells. To achieve this, the drug discovery technology unit has screened its structure-enriched Phylomer libraries to discover novel cell penetrating peptides (CPPs). Screening Phylomer libraries displayed on phage identified a diverse pool of hundreds of phylomers with cell penetration activity. As anticipated, some of these peptides showed strong similarities to known classes of CPP-like sequences, particularly the positively charged TAT-like class of arginine-rich peptides. The majority of sequences however bore no resemblance to any of the well-characterised CPP classes, supporting the notion that phage-displayed Phylomer libraries represent a rich source of novel cell-penetrating peptides. Assessment of synthetic phylomer peptide uptake into cells revealed a functional hit rate of 11% with some peptides exhibiting cell-specific uptake. Importantly, uptake into cells was also observed when some of these peptides were expressed recombinantly as fusions to the maltose-binding protein (MBP). These data suggests that recombinant peptides may not only exhibit cell-penetrating activity, but that they may also facilitate transport of a large protein cargo into cells. Currently, our collaborations with Roche have been extended to further validate the potential of one particular cell-penetrating phylomer peptide for delivery of biologics drugs across the blood brain barrier.

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

The CD40L receptor on T-cells is critical for many inflammatory diseases, including Asthma, Inflammatory

Bowel Disease, Rheumatoid arthritis and Lupus. 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.

### DISCOVERING AND VALIDATING NEW TARGETS USING 'PROTEIN INTERFERENCE'

(Collaboration with Cambridge University)

The Drug Discovery Technology Unit has been collaborating with the distinguished Professor of Oncology Ashok Venkitaram of the Hutchison MRC Unit at the University of Cambridge in the UK. The objective 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 used to identify the target can be used to validate the target via 'protein interference'. It is expected that this protein-level target validation will be very useful as it provides an opportunity to block disease-relevant interfaces of target proteins while not blocking their normal functions. To commercialise this opportunity, a new company name 'Phenomica' has been created as a joint spin-off between

Phylogica and the University of Cambridge

### TARGETING THE 'SONIC HEDGEHOG' PATHWAY TO DEVELOP CANCER THERAPEUTICS

Interference with key components in the Sonic Hedgehog (SHH) signalling pathway by mutation or over-expression is associated with a number of cancers. Following on from the success of the first collaboration, the Drug Discovery Unit has embarked on a second collaboration with the Hutchison/MRC Unit at the University of Cambridge to screen Phylomer libraries for peptides that can target this pathway and, ultimately, potentially inhibit tumorigenesis. Genetic screens in the Drug Discovery Unit have identified several Phylomers that can bind these targets, and these will be tested for their ability to affect cancer cells in culture. At the MRC Hutchison Institute, a novel screening technique has been developed to compliment this approach, which is currently in the process of being patented. This research also involves a local collaboration with our TICHR Brain Tumor Group, who are interested in exploring such Phylomers as potential therapeutics in their paediatric brain tumour models.

### DISCOVERING NEW ANTIMICROBIALS AGAINST MULTI-RESISTANT MICROORGANISMS (COLLABORATION WITH MEDIMMUNE)

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. The collaboration with Medimmune was to identify and characterize antimicrobial phylomers 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 biophysical

properties of antimicrobial Phylomer peptides by a technique known as circular dichroism. These studies measure the extent of formation of the 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 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 broths), and have identified Phylomer derivatives which are more active than a potent antimicrobial peptide known as Tachyplestin which is isolated from the horse-shoe crab.

## Staff and Students

### HEAD OF DIVISION:

Paul Watt Bsc (Hons), D Phil  
Honorary Research Fellow at Telethon Institute for Child Health Research  
Adjunct Professor at the school of Paediatrics and Child Health of University for Western Australia.  
Non-executive director of ASX listed Avita Medical Limited

Richard Hopkins BSc (Hons), PhD  
Head of Internal Research – Drug Discovery

### TEAM LEADERS

Katrin Hoffmann BSc (Hons), PhD [Cell Penetrating Peptide Discovery/Phage]  
Nadia Milech BSc (Hons), PhD [Intracellular Projects and Target Discovery]  
Colin Thompson BSc (Hons), PhD [Bioengineering]  
Shane Stone BSc (Hons), PhD [Structural Biology/Modelling & Bioinformatics]  
Paula Cunningham BSc (Hons), PhD [Inflammation and Bioassay Development]  
Tatjana Heinrich BSc (Hons), PhD [Antimicrobial Discovery]

### RESEARCH STAFF:

Mark Anastasas BSc (Hons)  
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\*Lan Doan BSc (Hons)  
Geoff Doherty BSc (Hons), PhD  
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\*Rebecca Hellsten BSc (Hons)  
Suzy Juraja BSc (Hons), MSc, PhD  
Maria Kerfoot BSc (Hons)  
Karen Kroeger BSc (Hons), PhD  
Brooke Longville BSc (Hons), PhD

# Drug Discovery

Marie Scobie BSc (Hons)  
Sarah See BSc (Hons), PhD  
Yew-Foon Tan BSc (Hons,) PhD  
Susan Turner BSc (Hons)  
Scott Winslow BSc (Hons)

## SUPPORT STAFF:

Leanne Neville  
Farzana Khan BSc

## External Committees

### INTERNATIONAL

Prof Paul Watt

Cambridge Healthtech Institute Conference Faculty for  
PepTalk, San Diego

Conference faculty IBC Protein Engineering Summit/Beyond  
Antibodies, San Francisco

### NATIONAL

Member of Western Australian Committee of Ausbiotech

Member of the 'Pathfinder' Commercialisation Grant Panel,  
University of Western Australia

## Invited Presentations

### PROF PAUL WATT

Jan 11 -15, CHI PepTalk, San Diego

Feb 1-4, International Conference on Drug Discovery and  
Therapy, Dubai

Feb 11-12, Sachs Investor Forum, Zurich, Switzerland

March 2-4, Queensland Protein Symposium, Brisbane

April 11-12, Natural Peptides To Drugs (N2PD)

Zermatt, Switzerland

June 21-23, IBC Beyond Antibodies, San Francisco USA

June 28-30, Windhover EuroBiotech Forum Paris France

June 22-24, Bioshares Biotech Summit, Thredbo, New South  
Wales

August 5-9, European Peptide Symposium, Copenhagen  
Denmark

October 10-12, Biopartnering Europe, London

Oct 27-28, Oxford Global 2nd Annual Proteins Congress, Berlin

## Overview

Research in the Genetics and Health Laboratory (GHL) at TICHR is mostly about understanding genetic risk in disease and how this influences, or is influenced by, environmental risk factors. We also do research that is primarily designed to lead us to novel vaccine candidates for parasitic infection. Senior members of the GHL, Jenefer Blackwell, Sarra Jamieson and Christopher Peacock, have had a long term interest in infectious disease, particularly bacterial and parasitic diseases. At TICHR the group has established family studies of ear infection in non-Indigenous children in Western Australia (WA) and of ear health and metabolic diseases including type 2 diabetes (T2D) in a WA Aboriginal population. We are also using genetics, gene expression and studies of metabolism to understand why T2D is a major risk factor for bacterial sepsis in Thailand. Sarra Jamieson, who leads the ear health studies, also has a major interest in epigenetic regulation of genes that influence susceptibility to complex disease, and is applying this approach to understand the increased incidence of hypospadias in Australian boys. Jenefer Blackwell, Head of the GHL, retains a position as Honorary Senior Scientist and Affiliated Principal Investigator at the Cambridge Institute for Medical Research (CIMR), University of Cambridge, UK, allowing her to maintain a small laboratory in Cambridge which focuses on host genetics and parasitic disease research. Christopher Peacock focuses his research on understanding more about genetics of bacterial and protozoan pathogens. During 2009 he was awarded an ARC Future Fellowship which has allowed him to establish an independent laboratory in the School of Biomedical, Biomolecular & Chemical Sciences at UWA. He retains an honorary position at TICHR and maintains close ties with the GHL. His collaborative projects with the GHL are included in this report, as are the projects from the CIMR laboratory.

Core funding – The Stan Perron Charitable Foundation, The Western Australian Government, and The University of Western Australia

## Genetics of Complex Disease

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

Jenefer Blackwell (Project Leader), Harvey Coates, \* Heather Cordell, Elizabeth Davis, Sarra Jamieson, Simon Miles, Marie Rye, Elizabeth Scaman, Genevieve Syn, Shyan Vijayasekaran (\* International Partner)

Understanding health and disease in Aboriginal communities could play an important role in reducing the disparity between Aboriginal and non-Aboriginal populations in Australia. The aim of this project is to use genetics as a tool to understand more about the pathogenesis of disease in Aboriginal Australians. During 2008 a partnership was established between the Ngangganawili Aboriginal Health Service (NAHS) and TICHR, underpinned by the signing of memoranda of understanding (MoU) between NAHS and TICHR, and between NAHS, Karalundi Aboriginal Educational Community Inc. (KAEC; which is serviced clinically by NAHS) and TICHR. These MoUs incorporate the principles for research in Aboriginal communities as outlined within the framework of the NHMRC and other national guidelines. The family study of ear health and metabolic diseases was approved by the WA Aboriginal Health and Information Ethics Committee (WAAHIEC) in 2009.

This study is examining genetic susceptibility to otitis media in children, and genetic risk factors for metabolic diseases such as type 2 diabetes (T2D), heart disease, renal failure, and obesity in adults. Collection of saliva for DNA commenced in November 2009, and by mid 2010 we had 425 fully consented DNA samples from large inter-related pedigrees which have been analysed on the Illumina 1.5M Duo SNP-chip to allow genome-wide association study (GWAS) of these diseases and related clinical and quantitative trait data. Preliminary analysis of body mass index and T2D has identified regions of association containing genes with strong functional implications for T2D in this population, results of which will

be published following a major feedback to community and educational project being undertaken in June 2011. Other traits are under analysis. The results of these studies should be broadly applicable to other WA Aboriginal communities, and could inform treatment and translational research strategies across Aboriginal and Torres Strait Islander communities.

Funders of the project: The NHMRC

### CANDIDATE GENE AND GENOME-WIDE ASSOCIATION STUDIES OF OTITIS MEDIA

Sarra Jamieson (Project Leader), Jenefer Blackwell, \*David Burgner, Harvey Coates, Tim Cooney, Richard Francis, Francis Lannigan, Joyce Oommen, Peter Richmond, Marie Rye, Elizabeth Scaman, Shyan Vijayasekaran, Selma Wiertsema (\* National Partner)

Otitis media (OM) is characterised by inflammation of the middle ear cavity. OM affects almost every child at least once by school age with up to 40% of children suffering recurrent episodes of OM (rOM;  $\geq 3$  episodes in 6 months or  $\geq 4$  episodes in 12 months). Recurrent episodes of OM require surgical intervention and can result in conductive hearing loss that affects language development. Heritability studies confirm a substantial genetic component in addition to a role for environmental factors in susceptibility to the broad clinical spectrum of OM. This study aims to further our understanding of both the genes and the environments that are play in role in susceptibility to childhood OM. To do this we are using two independent cohorts; the first is the WA Family Study of OM (WAFSOM; <http://www.ichr.uwa.edu.au/om>), this study has recruited around 820 families where the children are diagnosed with rOM in addition to their parents and any affected siblings. Secondly, we are using data from the WA Pregnancy Cohort (Raine) Study, a longitudinal birth cohort of 2868 children for whom there is clinical assessment and parental questionnaire data that indicates 644 children had

OM in their first three years of life.

To understand the environmental factors that predispose children to recurrent or severe OM we are using the Raine Study parental questionnaire data from years 1-3. We have shown that there a number of environmental factors associated with an increased risk of OM in early childhood. This includes the attendance of day care at age 1-3 years, with children who do attend daycare nearly two times more likely to suffer recurrent OM (Odds ratio [OR]=1.74; P=1.03x10<sup>-5</sup>; 95% CI=1.36-2.26). Children with OM are also more likely to have been diagnosed with allergy in years 1-3, 37% of children with OM were also diagnosed as allergic compared to 29% of children without OM (OR=1.47; P=0.0005; 95% CI=1.18-1.81). Other environmental variables, including breastfeeding duration, low birth weight, environmental tobacco smoke exposure, pet exposure, maternal education and income were not associated with an increased risk of OM in this population.

To identify the genes that contribute to rAOM we have employed candidate gene and genome-wide approaches. Results from a candidate gene analysis using samples collected as part of the WAFSOM Study and the Raine Study show that variants in the FBX011 gene are associated with recurrent and severe OM in childhood (P<sub>combined</sub>=2.98x10<sup>-6</sup>). Together, the results from these investigations confirm that FBX011 gene plays an important role in childhood susceptibility to rAOM. We are now looking at how this gene may be involved in rAOM, this includes analysis of the gene's expression profile in epithelial cells of the middle ear and respiratory tract. We are also carrying out the first genome-wide association study (GWAS) to identify genes involved in OM susceptibility. We are doing this using Illumina 660 Quad SNP-chip data available for 1500 of the Raine Study participants. The results of this GWAS are expected soon.

Funders of the project. The Raine Medical Research Foundation, University of Western Australia, The Brightspark Foundation

## METAGENOMIC STUDY OF PATHOGENS ASSOCIATED WITH OTITIS MEDIA

\*Christopher Peacock (Project Leader), Sarra Jamieson (Project Leader), Harvey Coates, Richard Francis, Lea-Ann Kirkham, Ace Choo Leng, Peter Richmond, Elizabeth Scamen, Selma Wiertsema, Shyan Vijaysekaran (\*National Partner at UWA and Honorary Scientist at TICHR)

One of the main factors involved in the incidence and severity of acute otitis media (AOM) is the presence of otopathogens made up of a range of bacteria and viruses in the normally pathogen free environment of the middle ear. Inflammation and the subsequent clinical symptoms result from the host's response to the presence of these organisms. Although there are three known bacterial pathogens commonly found in patients with AOM, the nature of the mechanism involved and the diversity of bacterial colonization of the middle ear is poorly understood. OM is the commonest condition in children treated with antibiotics below the age of 3, their effectiveness is limited. This is thought mainly to be due to the complex relationship of multiple species within a bacterially generated matrix called a biofilm.

This study is using the latest advances in sequencing to determine the complete microbial diversity within the middle ear of AOM patients together with paired samples from the nasopharyngeal region, considered the source of contamination pathogens prior to the onset of disease. This project is examining the incidence and relationship of both bacterial and viral organisms including the complex interaction of both commensal and pathogenic species. Bacterial diversity will be assessed using the amplification of the 16S ribosomal locus that is commonly used to determine microbial diversity. Greater detail of the mechanisms involved will be determined from the whole genome sequencing of bacterial and viral nucleic acid purified from the middle ear and nasopharyngeal samples taken by surgeons during the process of ventilation tube insertion. This will help identify specific genetic determinants involved in inducing

inflammation within the middle ear during OM.

## GENOME-WIDE ASSOCIATION STUDY OF VISCERAL LEISHMANIASIS

Jenefer Blackwell (Project Leader), \* Heather Cordell, Michaela Fakiola, Richard Francis, \* Muntaser Ibrahim, \* Selma Jeronimo, Sanjana Mehrotra, E. Nancy Miller, Anshuman Mishra, Joyce Oommen, \* Shyam Sundar, \* Mary Wilson (\* International Partners)

The parasitic disease Kala-azar or visceral leishmaniasis, caused by members of the *Leishmania donovani* species complex, is associated with liver, spleen and lymph gland enlargement, fever, weight loss, anaemia, and is fatal unless treated. Three major foci of VL occur in India, Sudan and Brazil, and children are the most prominently affected. Importantly, 80-90% of human infections are sub-clinical or asymptomatic, usually associated with strong cell-mediated immunity (positive skin-test delayed type hypersensitivity (DTH); lymphocyte proliferation; interferon- $\gamma$  T-cell response) to leishmanial antigen. Understanding why two people with the same exposure to infection differ in susceptibility could provide important leads for improved therapies.

During 2008-2010 we undertook a GWAS of visceral leishmaniasis and the quantitative DTH trait using 4880 DNAs (India, Brazil, Sudan) genotyped on the Illumina 660 Quad chip as part of phase 2 of the Wellcome Trust Case Control Consortium (WTCCC2), with deep replication in a further 1000 cases and 1000 controls from India. A single major peak of association that crossed the epidemiological divides of parasite species and geography was in the HLA Class II gene region (combined P=2.22x10<sup>-16</sup>). Ongoing projects in the lab are designed to determine precisely how the Class II region gene involved is determining disease risk versus protection, knowledge of which is also being applied to vaccine development.

Funders of the project. The Wellcome Trust and the NIH

### GENETICS AND METABOLOMICS AT THE INTERFACE BETWEEN TYPE 2 DIABETES AND INFECTION IN THAILAND

Jenefer Blackwell (Project Leader), \*Gregory Bancroft, Surachat Bhuddisa, \*Saskia Decuypere, Richard Francis, Sarra Jamieson, Prasong Khaenam, \*Sunee Korbrisate, \*Ganjana Lertmemonkolchai, \*Malcolm McConville, Joyce Oommen, Christopher Peacock, Narin Intaluck (\*International and National Partners)

In this project, we have brought together a team of scientists from Thailand and Australia, supported by key collaborators from the UK, to tackle the important problem of sepsis caused by *Burkholderia pseudomallei* and other bacterial pathogens in Thailand, and the role that T2D plays as a risk factor for severe disease. The underlying strategy for this project is to use a combination of genetics, transcriptomics and metabolomics to understand the interaction between T2D and sepsis, especially melioidosis, in Thailand. A successful bid for local funding in Thailand supported collection during 2008/2009, which has achieved a total sample of: (1) 764 T2D with sepsis; (2) 775 T2D alone; (3) 450 sepsis alone; (4) 661 healthy controls. Pilot candidate gene analyses based on the output of available transcriptome data and on the hypothesis that iron metabolism genes influence disease outcome is ongoing, as are pilot studies comparing the metabolome in blood samples from the 4 different phenotypic groups. Further funding proposals to support this research are under consideration. Overall, the combination of results of host genetic, transcriptomic and metabolomic data will help to define immunological, biochemical, metabolic, and molecular pathways that are important in determining heritable and environmental risk, pathogenesis, and the interplay between T2D and sepsis.

Funders of the project. Commission for Higher Education, Thailand

## Epigenetic Mechanisms of Complex Disease

### THE EPIGENETICS OF HYPOSPADIAS

Sarra Jamieson (Project Leader), \*Natasha Nassar (Project Leader), Andrew Barker, Richard Francis, Tereena Lucas, Joyce Oommen, Naeem Samnakay, Elizabeth Scaman (\*National Partner at USYD, Honorary Scientist at TICHR)

Hypospadias is a congenital malformation of the male genitalia whereby the urethral opening develops on the ventral (underside) surface of the penis, or on the scrotum or perineum as a result of abnormal urethral closure between 8 and 14 weeks gestation. Most hypospadias cases require major surgical repair at 1 year to ensure urinary function and fertility in the long term. Research carried out at TICHR by Dr Natasha Nassar indicates that, in Western Australia, hypospadias is the second most common birth defect among boys affecting, 1 in every 130 male infants, with rates doubling over the last 25 years. The aetiology of hypospadias is largely unknown, but an underlying disturbance in endogenous hormone production has been identified as a key causal mechanism. Preconceptional (maternal or paternal) or in utero (maternal) exposure to endocrine disrupting chemicals (EDCs), environmental agents with oestrogenic or anti-androgenic effects, has been proposed as a potential risk factor. To date the precise biological mechanisms of action of EDCs remain to be elucidated, however, research in animals with genital anomalies suggests that an alteration of epigenetic modifications might be important.

In 2009, The Understanding Hypospadias Study (<http://www.ichr.uwa.edu.au/hypospadias>) was established. This study is currently recruiting boys who have been diagnosed with hypospadias (cases) and boys who are undergoing circumcision for non-medical reasons (controls), plus their parents. At the time of surgery for hypospadias repair or

circumcision, and with full parental consent, we collect a small piece of the excess prepuce tissue that would normally be discarded plus a small blood sample. From these samples we extract DNA, to look at epigenetic modifications (specifically DNA methylation) and RNA, to look at gene expression. The DNA methylation and gene expression profiles are then compared between cases and controls to identify genes that show differential regulation or expression levels. To date we have recruited around 30 boys undergoing hypospadias repair and 22 boys undergoing elective circumcision to the project. Preliminary results from this study have shown a trend towards increased expression of several genes, specifically ATF3, CTGF and CYR61, in hypospadias vs. normal prepuce tissue. These results are currently being followed up in larger number of samples. We also have funding proposals are under consideration to carry out both genome-wide methylation and genome-wide gene expression analyses in these samples.

Funders of the project. Cancer Research Council, University of Western Australia

### THE EPIGENETIC REGULATION OF A WOUND HEALING GENE INVOLVED IN CUTANEOUS LEISHMANIASIS

Sarra Jamieson (Project Leader), \*Lea Castellucci (Project Leader), Jennie Blackwell, \*Edgar Carvalho, Ace Yu Leng Choo, Joyce Oommen, Christopher Peacock (\*International Partners)

Cutaneous leishmaniasis is a parasitic disease caused by *Leishmania braziliensis* in South America. It is characterised the development of localised cutaneous lesions that, in a fraction of patients, can develop into a mucocutaneous form that may result in destruction of the nasopharyngeal membranes. Previous research in a cutaneous leishmaniasis mouse model identified the Fli1 gene as playing a role in enhanced wound healing and resistance to leishmania infection. In the resistant mouse cutaneous lesions heal rapidly and there is a down-regulation of the Fli1 gene in

macrophages. This down-regulation of Fli1 is not observed in the susceptible mouse where lesions fail to heal and progress to a chronic condition. This suggests that Fli1 is important in the wound healing response to *Leishmania braziliensis* infection. Following on from this work in the mouse model we have recently shown that the human homologue of this gene (FLI1) is significantly associated with cutaneous leishmaniasis in a Brazilian population (Castellucci et al, 2011). Given the genetic association of FLI1 with cutaneous leishmaniasis we hypothesised that the FLI1 gene will show differential expression and/or DNA methylation profiles following leishmania infection of human macrophages.

To test this we have infected a human macrophage cell lines with *L. braziliensis* parasites in vitro over a time course of 120 hours. DNA and RNA are harvested at specific time points for methylation and gene expression analysis. Preliminary results show a decreased expression of FLI1 over the infection time course, consistent with the data from the mouse model, with a  $\rightarrow$ 15-fold decrease in expression from 24 to 72 hours post infection. Preliminary analysis of DNA methylation levels at the FLI1 promoter CpG island following infection reveals an increase in hypermethylated DNA levels between 48 and 72 hours, indicating a change towards a transcriptionally repressive conformation at the FLI1 promoter. These preliminary results indicate that the decrease in FLI1 expression levels has an epigenetic origin. Funding proposals are currently under consideration to assess FLI1 expression and DNA methylation profiles in biopsies from cutaneous leishmaniasis patients.

### Parasite Genomics and Vaccine Studies

#### COLLABORATIVE DEVELOPMENT OF A VACCINE AGAINST CUTANEOUS AND VISCERAL LEISHMANIASIS

Jenefer Blackwell (Project Leader), \*Diane McMahon-Pratt, \*Mary Wilson  
[\*International Partners]

*Leishmania* are protozoan parasites that cause severe and debilitating cutaneous, as well as fatal visceral, disease in sub-tropical/tropical regions of Old and New Worlds. There are no vaccines in routine use. Despite the need for vaccines, there are challenges facing *Leishmania* vaccine development: (1) to find a vaccine that will cross-protect against the different forms of disease [i.e., visceral, cutaneous, or mucosal leishmaniasis]; (2) to induce long-lasting immunity, and (3) to identify key immune responses in vaccine-induced protective immunity. This project represents a collaborative effort between three laboratories working on the unified theme of vaccine development against leishmaniasis. In Cambridge, the Blackwell laboratory used DNA vaccination in mice to screen 100 unique *Leishmania* genes as vaccine candidates against high dose virulent *L. major* infection. Fourteen novel and reproducibly protective antigens were identified. Mary Wilson's lab at the University of Iowa discovered six novel antigens through cDNA library screening with immune serum and T cells. At Yale University, Diane McMahon-Pratt's lab had 4 well-characterized antigens which protected against *L. amazonensis* and/or *L. infantum* infection. During 2009 worked continued to determine which of a selection of 20 of these novel antigens are cross-protective against cutaneous and visceral Old World and New World *Leishmania* spp. in mice, and to determine whether alphaGalCer used as adjuvant with DNA enhances protective immune responses and vaccine efficacy. Peptide pools for 10 of these vaccine candidates were also used as antigens in antibody and T cell assays in blood samples taken from dogs or humans naturally infected with *L. infantum chagasi* in Brazil. By looking at the antibody and cytokine profiles associated with active or cured disease, and in dogs or humans exposed but resistant to infection, we are beginning to build a picture as to which antigens elicit potentially protective immune responses in dogs and humans. This has now been extended to study all 20 antigens, and to study humans naturally infected with *L. donovani* in India. Ultimately, the combination of murine, canine and human data will be used to determine the best cocktail of these antigens

to be taken forward into canine and/or human trials to reduce the incidence of human disease.

Funders of the project. NIH.

#### IMMUNOGENICITY AND EFFICACY TRIALS OF A DNA/MVA VACCINE AGAINST CANINE LEISHMANIASIS

Jenefer Blackwell (Project Leader), \*Orin Courtenay (Project Leader), \*Maria Antoniou, \*Diane McMahon-Pratt, Christopher Peacock, \*Mary Wilson  
[\* International Partners]

Studies in the Cambridge lab identified prime/boost vaccination with DNA/Modified Vaccinia virus Ankara (MVA) using the leishmanial antigen tryparedoxin peroxidase (TRYP) as the most protective vaccine producing long term immunity in mice. During 2009 papers were published that address the first major aim of this study which was to conduct safety (Phase I) and immunogenicity (Phase IIa) trials of a DNA/MVA TRYP *Leishmania* vaccine in kennel dogs. Funding proposals are under consideration to conduct a community-based Phase IIb/III field trial to reduce canine zoonotic visceral leishmaniasis infection, disease and infectiousness in a genetically diverse population of dogs exposed to natural infection with *L. infantum* on Crete. Phase III outcomes include clinical disease, parasite load as a marker of infectiousness to sand flies, and immunological correlates of these end points (in vitro cytokine stimulation assays, serology, and tissue cytokine mRNA expression). Analysis will show differences in the incidence of infection and clinical disease between fully blinded and randomized vaccine and control groups, and related to measured immunological responses. A successful canine vaccine will protect dogs against *Leishmania* infection and/or disease, and reduce or eliminate infectiousness of the reservoir host, thereby reducing or preventing transmission to humans.

Funders of the project: Pfizer Inc.

## INTEGRATED MULTIDISCIPLINARY STUDY TO DEFINE HUMAN HOST-TRYPANOSOMATID INTERACTION

\*Kenneth Gollob (Project Leader), \*David Anderson, \*Walderez Dutra, \*Kent Lohman, \*\*Christopher Peacock, \*Carolyn Talcott, \*Denong Wang  
(\* International Partners, \*\* National Partner at UWA and Honorary Scientist at TICHR)

The related intracellular protozoal pathogens *Leishmania* and *Trypanosoma cruzi* cause devastating diseases affecting millions of people throughout the tropics and sub-tropics. The conditions, leishmaniasis and Chagas disease, are considered some of the most neglected in terms of drug and vaccine development. The rapid advances in high-throughput data generation and global analysis of genome sequencing, transcriptomics, proteomics and glycomics has led to the possibility of studying the complex host pathogen interaction at the micro level. This will help determine the mechanisms involved in disease susceptibility. Given the almost infinite numbers of parasite and host factors and regulatory mechanisms at the genome, RNA transcript and protein level, studies need to be designed to take a non-hypothesis driven approach to identifying the critical elements involved in disease susceptibility.

This study is using a combined strategy of high throughput data generation on both host and parasite transcriptome, proteome and glycome to identify key host and pathogen signatures that can be used to discover novel therapies, vaccines and diagnostics. Three diverse species of *Leishmania* representing self resolving cutaneous, fatal visceral and non-human mammalian leishmaniasis will be compared during the early stages of infection, proliferation within and destruction of the host cells. We will also look at the mechanisms of the related intracellular pathogen *T. cruzi* for shared pathogenic determinants. In addition we will further define the interaction between parasite and host using High Throughput Cell Interaction Screening System (HiTCISS) to measure immunoregulatory macrophage profiles and parasite killing.

## COMPARATIVE ANALYSIS OF HUMAN AND KANGAROO LEISHMANIA: DEFINING HUMAN PATHOGENICITY GENES

\*Christopher Peacock (Project Leader), Audrey Appudurai, Jenefer Blackwell, Ace Yu Leng Choo, Wei Lu, Richard Francis, Rohini Gupta, Sarra Jamieson  
(\*National Partner at UWA and Honorary Scientist at TICHR)

Leishmaniasis is a major global disease that affects millions and kills many thousands of people. There are no vaccines, prophylaxis and the few drugs that are available are toxic and difficult to deliver. This project is using the non-human pathogenic strain of leishmania recently discovered in Australian marsupials as a model to identify and characterize genes that determine pathogenicity in humans. During 2009 work commenced on sequencing the genome of the kangaroo leishmania, data from which is being compared to the publicly available genomic sequences for species representing the full spectrum of human disease. Genes identified in pathogenic but not non-pathogenic leishmania will be cloned and transfected into the kangaroo leishmania and the transfected parasites studied for their effects in vitro in human cells and in vivo in mice. Kangaroo leishmania overexpressing known candidate vaccine antigens will also be used to develop a potential attenuated vaccine that will be tested in the mouse model of infection.

Funders of the project. NHMRC and ARC Future Fellowship

## Staff and Students

### HEAD OF DIVISION

Jenefer M. Blackwell BSc(Hons), PhD, FMedSci, DSc (Khartoum and Cantab)  
Professor in Genetics and Health, University of Western Australia  
Head, Division of Genetics and Health, Telethon Institute for Child Health Research, WA  
Honorary Senior Scientist and Affiliated Principal Investigator, Cambridge Institute for Medical Research, Cambridge, UK

### RESEARCH STAFF

Genetics and Health Lab:

Michaela Fakiola BSc(Hons), MSc (Health & Env't), PhD  
Sarra Jamieson BSc(Hons), MSc (Med Genet), PhD  
Joyce Oommen BSc, MSc (Biol Sci), Dip Bioinf, MSc (Immunol)  
Elizabeth Scaman BA(Hons)  
Genevieve Syn BSc(Hons)

UWA Lab:

Christopher Peacock BSc, FIMLS, PhD  
Ace Yu Leng Choo BSc(Hons), MSc  
Wei Lu BSc(Hons), PhD

CIMR Lab:

Michaela Fakiola BSc(Hons), MSc (Health & Env't), PhD

### POSTGRADUATE STUDENTS

Audrey Appudurai BSc, Honours Candidate (UWA, Peacock Lab)  
Surachat Buddhisa BSc(Hons), MSc, PhD Candidate (Thailand)  
Richard Francis BSc(Hons), MSc, PhD Candidate (UWA)  
Rohini Gupta BSc(Hons), Masters Candidate (UWA, Peacock Lab)  
Tereena Lucas BSc Honours Candidate  
Sanjana Mehrotra BSc(Hons) PhD Candidate (India)  
Anshuman Mishra BSc(Hons) PhD Candidate (India, CIMR Lab)  
Marie Rye BSc(Hons) PhD Candidate (UWA)

Narin Intaluck BSc(Hons), MSc, PhD Candidate (Thailand)

## Awards

Jenefer Blackwell, Honorary DSc, University of Khartoum, The Sudan

Jenefer Blackwell, ScD, University of Cambridge, UK  
Christopher Peacock, ARC Future Fellowship

## External Committees

### INTERNATIONAL

Jenefer Blackwell, Management Committee, Wellcome Trust Case Control Consortium Phase 2

Jenefer Blackwell, Publications Committee, Wellcome Trust Case Control Consortium Phase 2

### NATIONAL

Jenefer Blackwell, Chairman NHMRC Fellowships Panel, 2009 and 2010

### LOCAL

Sarra Jamieson, WA DNA Bank Management Committee, 2009+

Sarra Jamieson, Treasurer, Perth Epidemiology Group, 2008+

## Invited Presentations

### JENEFER BLACKWELL

2010 Second meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Co-convener and Speaker, 11-14 February 2010, Varanasi, India.

2010 Indigenous Genetic Research Roundtable, the Lowitja Institute, University of Melbourne, Invited Speaker, 2 July 2010, Melbourne, Victoria, Australia.

2010 Genetic Epidemiology and Population Health Symposium, Western Australian Department of Health, Invited Speaker and Summing Up Session Chair, the University of Western Australia Boat Shed, 12 July 2010, Crawley, Western Australia.

2010 ICOPAXII International Congress of Parasitology, Invited Session Chair, 15-20 August, Melbourne, Victoria, Australia.

2010 Symposium on High Throughput Approaches in Infection and Immunity, Invited Speaker, 7-9 December 2010, Cha-Am and Hua-Hin, Thailand.

2011 Third meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Co-convener and Speaker, 7-10 February 2011, Varanasi, India.

### MICHAELA FAKIOLA

2010 ICOPAXII International Congress of Parasitology, Invited Speaker, 15-20 August, Melbourne, Victoria, Australia.

2011 Third meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Invited Speaker, 7-10 February 2011, Varanasi, India.

### SARRA JAMIESON

2010 OTIGEN Consortium Meeting. Invited presentation. June 8th, Pamplona, Spain.

2010 OMOZ 2010-Australian Otitis Media Workshop. Invited presentation. May 25th-26th 2010, Darwin, Australia.

2011 Biochemistry Seminar Series. Invited presentation. May 21st, Perth WA

### CHRISTOPHER PEACOCK

2010 Infection and Immunity special meeting at the annual Australian Society of Immunology Conference, Perth, Western Australia

2010 12th International Conference on Parasitology (ICOPA), Melbourne, Australia

2010 AGRF meeting, Perth, Western Australia

2011 TMRC meeting on future Leishmania research, Salvador, Brazil.

## Overview

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 2010, we further detailed the cellular mechanisms by which UVB light is immunomodulatory. We had previously concentrated on the mechanisms involved when UVB was delivered prior to first allergen exposure. In 2010 we studied the ability of UVB to modulate responses in mice already pre-sensitised to allergens. In 2010, considerable attention was paid to the systemic effects of UV irradiation of skin on dendritic cell precursors in the bone marrow. Erythematous UVB irradiation of skin stimulated the production from bone marrow of tolerogenic dendritic cells. Further, UV-induced prostanoids were responsible for the effects of UV on dendritic cell precursors. We still do not know which cells are producing the prostanoids. In further studies, we have shown that inflammation of the respiratory system also induces the formation of tolerogenic dendritic cells from bone marrow by a prostanoid-dependent process.

In parallel studies we have investigated the effects of UV-induced vitamin D3 in control of immune cell activity and asthma models in mice. Humans obtain 90% of their vitamin D3 from UV irradiation of skin so it has been proposed by us, and others, that UV-induced Vitamin D3 may contribute to the immunomodulatory effects of UV. We have examined the effect of vitamin D3 in excess (painted onto the skin of mice with normal levels of vitamin D3) and in deficiency (mice were fed diets restricted in vitamin D3). We discovered that male vitamin D3-deficient mice were unable to respond to UVB irradiation of skin for vitamin D3 production. Thus, if the male mice responded to UVB for regulation of immunity, this was not via the modulatory properties of vitamin D3. This finding has given us an exciting and ongoing approach to

analyse the relative contribution of vitamin D3 and other UV-induced mediators to the immunomodulatory properties of UV irradiation.

In 2010, 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. These studies are ongoing.

## Projects

### IMMUNOMODULATORY EFFECTS OF UVB RADIATION ON INFLAMMATORY AIRWAYS DISEASE IN MICE

PH Hart, M Lambert, N Scott, DH Strickland

We have previously shown that UV irradiation of skin causes a systemic suppression of immune responses. We have analysed the effect of a single exposure to UV for a time equivalent to about 20 minutes in noon in summer in Perth. Experiments continued in mice sensitised to ovalbumin mixed with the adjuvant, alum. Our hypothesis was that UV-induced CD4+CD25+ T regulatory cells were responsible for reduced allergic airways disease. We extensively sought this cell in the trachea and lymph nodes of UV-irradiated, ovalbumin-sensitised mice at the time of allergen challenge (at least 3 weeks after UV-irradiation). Instead of a UV-induced CD4+CD25+ regulatory cell, we consistently detected more ovalbumin-sensitised effector CD4+CD25+ cells in the airway tissues. In 2010, attention switched to times closer to the time of UV irradiation, and the first (sensitising) exposure to OVA plus alum. In studies of lymph nodes draining the site of OVA plus alum intraperitoneal sensitisation, we detected a UV-induced, short-lived CD4+CD25+ regulatory cell that could be detected 7 days but not 21 days post-UV-irradiation. We also investigated the effect of UV delivered to the skin of OVA-presensitised mice. UV was again immunomodulatory but it

was necessary for the mice to be sensitised to a less intense sensitisation protocol. Studies are ongoing to gain a better understanding of the mechanism by which UVB radiation can modify some of the important pathological components of asthma, and the optimal time of UV delivery. These studies will contribute to a basic understanding of the immunological events in asthma development and how they can be modified by UV irradiation of skin.

Funded by NHMRC

### VITAMIN D IN EXCESS – EFFECTS OF TOPICAL VITAMIN D3

S Gorman, PH Hart

Skin keratinocytes have an autonomous vitamin D pathway and can produce substantial amounts of 1,25(OH)<sub>2</sub>vitamin D3, the hormonally active form of vitamin D3, when exposed to UVB light. We propose that levels of 1,25(OH)<sub>2</sub>vitamin D3 produced by keratinocytes and immune cells at the irradiated site may be involved in the immunomodulatory effects following acute UV exposure of skin. Hence we have studied the effects of 1,25(OH)<sub>2</sub>vitamin D3 applied directly to skin. The concentration of 1,25(OH)<sub>2</sub>vitamin D3 was based on studies in UV-irradiated human skin. Application on skin of 1,25(OH)<sub>2</sub>vitamin D3 enhanced the regulatory capacity of non-antigen-specific CD4+CD25+ cells in the draining lymph nodes. When purified from these nodes, and transferred into allergen-presensitised mice, the immune response in the airways of recipient mice to aerosolised allergens was reduced. The immune properties of CD11c+ dendritic cells from draining lymph nodes of mice topically painted with 1,25(OH)<sub>2</sub>vitamin D3 have also been studied. Upon adoptive transfer, they were less efficient at priming immune responses. We propose that these CD11c+ cells contribute to the reduced regulatory activity of CD4+CD25+ cells. However, gene arrays have also indicated that there are direct effects of 1,25(OH)<sub>2</sub>vitamin D3 on the regulatory abilities of CD4+CD25+ cells. These results suggest that 1,25(OH)<sub>2</sub>vitamin

D3 formed upon UV irradiation of skin may contribute to the immunomodulatory effects of UV irradiation of skin, as well as the enhanced health of our immune system.

Funded by Raine Foundation and the Asthma Foundation of WA

## VITAMIN D IN DEFICIENCY – EFFECT OF DIETS DEFICIENT IN VITAMIN D3

S Gorman, PH Hart, N Scott

One approach to study vitamin D3 deficiency is to obtain vitamin D receptor (VDR)  $-/-$  mice or CYP27B1  $-/-$  mice, i.e. mice unable to make 1,25(OH)<sub>2</sub>vitamin D3 from 25(OH)vitamin D3. However, both VDR  $-/-$  and CYP27B1  $-/-$  mice have serious developmental problems that lead to skeletal, reproductive and immune dysfunction. Further, serious discordance in phenotype between VDR  $-/-$  mice and CYP27B1  $-/-$  mice suggests that the VDR has ligand-independent effects. For these reasons, we have established colonies of wild-type BALB/c mice fed a vitamin D restricted diet. The ovalbumin-driven model of allergic airways disease has been established in these mice. Initial 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.

Funded by Raine Foundation

## VITAMIN D IN DEFICIENCY – EFFECT OF UV IRRADIATION OF SKIN

PH Hart, S Gorman, N Scott, S Bazely

When vitamin D3-deficient mice are UVB irradiated, only the female mice are able to respond with systemic vitamin D3 levels. We do not fully understand why male vitamin D3-deficient mice are unable to make circulating vitamin D3 although they are able to make vitamin D3 if it is provided in their diet. We proposed that this provided a powerful model

to determine which immunoregulatory responses measured following UVB irradiation of skin were vitamin D3-dependent. In assays of both systemic and local contact hypersensitivity, and OVA-induced asthma, male and female mice have responded to UV irradiation to a similar extent. We have not detected responses to UV in male vitamin D3-deficient mice that are vitamin D3-dependent. As part of his Honours project, Scott Bazely examined the skin architecture, and histological changes in response to UV irradiation, by skin of male vitamin D3-deficient and  $-replete$  mice. No changes could be linked with the inability of male vitamin D3-deficient males to respond to UV for vitamin D3-production.

## EFFECT OF UVB ON BONE MARROW-DERIVED DENDRITIC CELLS

R Ng, J Bisley, N Scott PH Hart.

In response to erythral amounts of UV, there is inflammation of the skin. Signals are then sent from the skin to the bone marrow, via the lymph nodes, such that new immune cells are produced that can be involved in the inflammatory response. The phenotype and function of cells isolated from the bone marrow of animals administered a single inflammatory dose of UV have been studied. Dendritic cells derived from the bone marrow of UV-irradiated mice were significantly less efficient at presenting antigen to T cells *in vivo*. They induced tolerance and results suggest the induction of regulatory cells. When the mice were implanted with slow release indomethacin pellets prior to UV-irradiation, the regulatory effects of UV on bone marrow CD11c<sup>+</sup> cells were removed. The effect of UV could be replicated by subcutaneous administration of slow release prostaglandin E2-containing pellets. We are studying the mechanisms by which UV-induced prostanoids regulate the development of tolerogenic CD11c<sup>+</sup> cells. Gene targeted arrays have identified molecules that are increased in CD11c<sup>+</sup> cells from bone marrow of UV-irradiated mice, but which are no longer present in bone marrow cells from mice treated with

indomethacin before UV irradiation. We are further analysing the identity and function of these molecules.

Funded by NHMRC, UWA Postgraduate Award to RN, Perron award to RN

## EFFECT OF EXPERIMENTAL ALLERGIC AIRWAYS DISEASE AND THE INFLAMMASOME ACTIVATOR, ALUM, ON BONE MARROW-DERIVED DENDRITIC CELLS

N Scott, J Bisley, R Ng, PH Hart.

In response to UV-induced inflammation of the skin, bone marrow derived dendritic cells are tolerogenic. 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 tolerogenic. Further their development is blocked by the administration of indomethacin and again suggests that inflammation-induced prostanoids are responsible. We propose that the formation of tolerogenic dendritic cells in the bone marrow is part of a homeostatic mechanism to limit the destructive properties of tissue inflammation.

Funded by NHMRC, UWA Postgraduate Award to RN, Perron award to RN

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

E 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

## Staff and Students

### RESEARCH STAFF

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

Shelley Gorman BSc (Hons) PhD

Misty Lambert BSc (Hons)

Naomi Scott BSc (Hons)

Jacqueline Bisley BSc (Hons)

### POSTGRADUATE STUDENTS

Eleanor Woodward BSc (Hons), PhD Candidate

Royce Ng BSc (Hons), PhD Candidate

Scott Bazely BSc, Hons Candidate

## Awards

### PRUE HART

Adjunct Professor, University of WA, NHMRC Principal Research Fellowship

### SHELLEY GORMAN

Raine Priming Grant

### SCOTT BAZELY

Honours 1st class, Murdoch University, Skin profiles in a murine model of vitamin D-deficiency

## Presentations

### PH HART

Invited symposium speaker, Australian Wound and Tissue Repair Society National Conference, Perth, March 2010.

Invited speaker, Day of Immunology, SCITECH, Perth, April 2010.

Invited speaker, Adelaide Womens and Childrens Hospital, Adelaide, June 2010.

Invited speaker, WABRI Seminar Series, Perth, August 2010.

Public Lecture, Perth Town Hall, October 2010. Series on Melanoma.

Invited symposium speaker, Australian Health and Medical Research Congress, National Conference, Melbourne, November 2010.

## External Committees.

### PH HART

Invited Member, NHMRC Academy

Invited Member, NHMRC RGMS working group.

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

Member, Cure Cancer Australia Scientific Committee

President, Australasian Society for Dermatology Research

Member, Organising Committee, Australasian Society for Immunology Annual conference, Perth, December 2010.

# 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.

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 Dean Bertolatti, Curtin; Dr Ian Gilmour, US EPA). 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).

Major highlights for the year include securing funding through the NHMRC Project Grant scheme and the CRC for Asthma.

## Early life determinants of lung growth

### VITAMIN D DEFICIENCY AND LUNG GROWTH

Graeme Zosky, Shelley Gorman, Prue Hart

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 (established by Dr Gorman and Prof Hart). 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.

Funding: NHMRC, Asthma Foundation of W.A.

### THE EFFECTS OF IN UTERO TOBACCO SMOKE EXPOSURE ON LUNG GROWTH AND HEALTH

Alexander Larcombe, Graeme Zosky, Rachel Foong, Peter Sly.

Unborn children exposed to tobacco smoke are more likely to suffer respiratory disorders such as bronchitis and wheeze and are more likely to be admitted to hospital for respiratory problems. Exposure to cigarette smoke before and directly after birth affect a child's lung function, however, a mother's smoking during pregnancy, rather than her smoking status after the birth is more highly correlated with the development of childhood asthma and wheeze. There is an association between in utero exposure to cigarette smoke to reduced lung function and childhood asthma, however the mechanisms for this are unknown.

This project began in 2008 when we characterized our commercially available cigarette smoking machine using adult mice. We showed that a regime of 3 cigarettes twice per day for 13 days was optimal for in utero cigarette smoke exposure studies.

Following characterization of the smoking machine, we began exposing groups of dams to mainstream cigarette smoke. Control dams were exposed to medical air only. When the resultant pups were two weeks old, we weighed them, measured their lung volumes, baseline lung function and lung mechanics over 20cm H<sub>2</sub>O inflation/deflation manoeuvres and assessed lung morphometry. We showed that two week old

mice exposed to cigarette smoke in utero were significantly smaller and had significantly lower lung volumes than control pups. As a result of their smaller size, cigarette exposed pups had significantly impaired lung function, although lung structure was not altered. These data were the first to show impaired lung function in mice exposed to tobacco smoke in utero using appropriate techniques.

Funding : Asthma Foundation of Western Australia New Investigator Grant.

## Respiratory environmental health

### ARSENIC INDUCED NON-MALIGNANT LUNG DISEASE

Kathryn Ramsey, Peter Sly, Graeme Zosky

The contamination of groundwater with arsenic (As) is a global health problem. In the Ganges Delta (West Bengal, Bangladesh) over 80 million people have been exposed to unsafe levels of As from shallow tube wells that were installed to prevent the epidemic of waterborne diseases in infants. This exposure event is a public health catastrophe and has been described as the biggest mass poisoning in human history. 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.

In 2010 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. Preliminary results from these studies suggest that the effects of arsenic and influenza infection are additive such that mice that received both exposures had the worst outcome. These respiratory deficits also persisted into adulthood demonstrating the importance of early life environmental and viral exposures in determining adult lung health.

Funding: NHMRC Project Grant

### REGIONAL ENVIRONMENTAL DETERMINANTS OF LUNG HEALTH

Graeme Zosky, Russell Wong, Catherine Boylen, Brian Devine, Fiona Maley, Angus Cook

Exposure to mining dust in towns close to open cut mines in Western Australia has been identified as 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 mining sites in Australia. We will determine whether exposure to dust in communities close to mines causes a level of inflammation in the lung that is of concern and also whether the response varies depending on the mineral/metal content of the dust. These studies will assist in informing public health and safety policy in these communities.

We have recently 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 PM10 (< 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. Additional groups of mice were exposed to 100 µg of 10 µm silica or inert polystyrene beads as controls for generic responses to inhaled particulate matter. To date we have completed the analysis of cell numbers (and type) from lavage samples from mice in all groups. The magnitude of the influx of inflammatory cells was dependent on the dose and sample used. The silica and polystyrene preparations resulted in a minor (barely detectable) inflammatory response. In contrast a significant influx of neutrophils (polymorphonucleocytes) was observed in the mice exposed to PM10 from both Kalgoorlie and Newman with a greater

# Lung Growth and Respiratory Environmental Health

response in mice exposed to PM10 from the latter. We are currently measuring cytokine levels in lavage fluid from these mice and have begun Phase 2 which involves exposing mice to samples from other sites and measuring lung function at key timepoints (6 hr, 24 hr and 7 days post-inoculation).

Funding: CRC for Asthma

**DIESEL EXHAUST PARTICLE EXPOSURE AND ITS EFFECTS ON LUNG FUNCTION AND EXACERBATIONS OF AIRWAYS DISEASE**  
Alexander Larcombe, Catherine Boylen, Graeme Zosky, Rachel Foong, Peter Sly.

This ongoing project is designed to directly address the issue of whether acute exposure to diesel exhaust particles (DEP) results in exacerbation of existing respiratory illness. In 2009 and 2010 we established a mouse model of acute 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 H2O 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 addition to the DEP/virus studies described above, a

secondary aim of this project will be to superimpose the newly developed mouse model of acute DEP exposure onto our already established mouse models of allergic airways disease (ie asthma). In this way we will be able to assess whether, and by what means, acute exposure to DEP will cause exacerbations of these respiratory illnesses.

## Mechanisms of airway hyperresponsiveness in asthma

### VIRAL INDUCED AIRWAY HYPERRESPONSIVENESS

Rachel Foong, Alexander Larcombe, Anthony Kicic, Steve Stick, Peter Sly, Peter Noble, 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 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.

Neutrophil elastase; We have shown previously that influenza induced AHR is due to disruption of the epithelial barrier resulting in increased access of bronchoconstrictor agents to the airway smooth muscle. Neutrophils are one of the primary response cells involved in the inflammatory response to influenza. Neutrophils release a number of key products including neutrophil elastase (NE) which, when in excess, can damage the lung tissue. We hypothesized that NE, by disrupting the epithelial barrier, was responsible for influenza induced AHR. To test this we used a genetically modified mouse which lacks neutrophil elastase (NE<sup>-/-</sup>). NE<sup>-/-</sup> mice and wild-type littermates were infected with influenza A and studied for inflammation, viral replication and lung function at the peak of the response (3-4 days post-infection). We

found that there was no difference in responses between the two groups of mice suggesting that NE is not involved in the induction of influenza related AHR.

DEP and influenza; As part of our ongoing interest in respiratory responses to environmental exposures we have developed and characterized a mouse model of acute DEP exposure. DEP is one of the major contributors to atmospheric particulate matter in urban areas. There are strong epidemiological associations between levels of particulate matter in the atmosphere and respiratory morbidity and mortality. One explanation for this observation may be DEP induced exacerbation of respiratory disease. In order to test this we exposed mice infected with influenza, at the peak of inflammation (day 4), to DEP and measured responses 6 hours later. We found that mice exposed to both DEP and influenza had higher levels of inflammation compared to mice exposed to either DEP or influenza alone. Additionally, DEP exposure increased viral titre suggesting that it enhanced viral replication. These studies are ongoing and we plan to extend the measurement timepoints to determine whether DEP exposure prolongs the resolution of influenza symptoms.

Funding: UWA Research Development Award

### EMERGING MODELS OF ASTHMA

Alexander Larcombe, Graeme Zosky, Peter Noble, Rachel Foong.

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 exposed adult BALB/c mice to 25µg HDM protein in saline daily for ten sequential days. 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. The 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. These mice showed significantly increased total IgE and eosinophilia, two key features of allergic airways disease.

One of the most striking abnormalities in patients with obstructive lung disease is a loss of the bronchodilation that normally occurs in healthy individuals when they take a deep inspiration (deep inflation, DI). In both asthma and COPD, the protective action of DI fails. It is argued that an impaired response to DI is intimately related to disease morbidity

including airway obstruction and airway hyperresponsiveness (AHR). The general aim of this on-going project is to examine the underlying mechanisms governing beneficial responses to DI and to determine the susceptibility of the system to interference in disease.

#### REGULATION OF AIRWAY CALIBER BY DEEP INSPIRATION IN HEALTH AND DISEASE

Peter Noble, Graeme Zosky, Alexander Larcombe, Russell Wong, Peter McFawn, Alan James, Howard Mitchell, Robyn Jones

The aim of our first study is to identify the mechanisms by which DI induced bronchodilation fails in humans using tissue from lung cancer patients. To achieve this objective we need to obtain both in vivo data from patients and in vitro data from tissue removed to treat their cancer. To date we have recruited 54 patients into the study. Bronchi from 24 patients were available for in vitro experiments using tissue removed following their surgery for lung cancer. We have established that the human airway wall dilates in response to simulated DI suggesting that beneficial responses observed in vivo are mediated by an intrinsic response to mechanical stretch. Bronchodilation to DI resulted in a substantial but transient reduction in airway responsiveness. We suggest that a failure of this beneficial response to DI could contribute to airway obstruction and AHR in disease. Our findings have now been published in the Journal of Applied Physiology (2011, doi:10.1152/jappphysiol.01226.2010) and have already attracted some interest in the form of a soon to be published editorial highlighting the importance of our findings (Lutchen & LaPrad).

The aim our second study is to characterise effects of DI induced prior to induction of bronchoconstriction. Whilst bronchodilatory effects of DI in humans were established in the mid 1900s, 'bronchoprotective' effects have only recently been documented. Recent studies show that DIs taken

before a bronchoconstrictor challenge attenuate subsequent bronchoconstriction (dubbed bronchoprotection) but the underlying mechanisms are unclear. The focus of an honours project (Russell Wong) was to use a mouse model to assess whether prior DI effects are due to reduced airway narrowing, reduced airway closure or enhanced bronchodilation to DI. Somewhat surprisingly prior DI effects did not modify airway narrowing or airway closure as predicted but instead enhanced bronchodilation to DI. The project has generated considerable data which will be published this year.

Funding: NHMRC and UWA Research Development Award

#### DEVELOPMENT AND CHARACTERIZATION OF NEW IMAGING TOOLS FOR THE ASSESSMENT OF MECHANICAL AND STRUCTURAL PROPERTIES OF AIRWAY AND LUNG TISSUE

Peter Noble, Robert McLaughlin, David Sampson, Bryden Quirk, Andrea Curatolo, Rodney Quirk, Jonathan Williamson, David Hillman, Peter Eastwood

Imaging technology has made a substantial and positive impact in the diagnosis and treatment of patients and is an effective tool in medical health research. The development of new imaging techniques promises future medical and research advances. Optical coherence tomography (OCT) is an imaging modality conceptually similar to ultrasound in that dimensional information is obtained from the reflection of light waves. The general aim of this on-going project is to test the utility of optical OCT as a tool in respiratory research.

The aim of our first study is to use anatomical optical coherence tomography (aOCT) a long scanning tool to measure different structural and mechanical properties of airways. Using an in vitro airway model (porcine) we demonstrated that aOCT could be used to effectively measure airway calibre, wall compliance and, importantly, morphology without the need for fixative agents. The study has generated numerous publications (JAP 108: 401-411, Respir Research 11:9, ERJ 35:

34-41).

The aim of our second study is to use a needle OCT to image lung tissue. The needle OCT differs from aOCT in that it has a reduced imaging depth but as a result a far greater resolution. We used an excised lung model (sheep) to determine the capacity for needle OCT to assess lung structure. Our initial experiments have been encouraging and we have shown that needle OCT can image individual alveoli. Our findings have been recently accepted for publication (Journal of Biomedical Optics).

## Staff and Students

### HEAD OF GROUP

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Senior Research Officer, Centre for Child Health Research,  
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### RESEARCH STAFF

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### POSTGRADUATE STUDENTS

Elizabeth Bozanich BSc(Hons) PhD Candidate  
Kathryn Ramsey BSc(Hons) PhD Candidate

### RESEARCH SUPPORT

Marina Stubbs

## Awards

Kathryn Ramsey, Maurice Blackburn International Travel Award

Kathryn Ramsey, Lung Institute of Western Australia Junior Medical Scientist Award

Kathryn Ramsey, Australia Society for Medical Research (W.A.) Murdoch Award

Kathryn Ramsey, Thoracic Society of Australia and New Zealand Travel Award

Rachel Foong, Thoracic Society of Australia and New Zealand Travel Award

Catherine Boylen, Thoracic Society of Australia and New Zealand Travel Award

## External Committees

### LOCAL

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

Graeme Zosky. Thoracic Society of Australia & New Zealand ASM Organising Committee.

Kathryn Ramsey. Thoracic Society of Australia & New Zealand (WA) Associates Committee.

Kathryn Ramsey. Thoracic Society of Australia & New Zealand ASM Organising Committee.

Peter Noble. Thoracic Society of Australia & New Zealand (WA) Associates Committee.

## Overview

Previous work of the Division of Molecular Biotechnology has identified the molecular nature of the house dust mite allergens and determined their IgE-binding hierarchy. Research in this area is now using pure recombinant allergens so reproducible investigation can be made to develop new prognostic tests and new types of immunotherapy. Similar studies for cat allergy have now identified the salivary allergens called Fel d 4, Fel d 7 and Fel d 8. IgE binding studies have now shown that for over half of adults with rhinconjunctivitis one of these allergens is more important than the Fel d 1 allergen hitherto considered to be of paramount importance. This has the potential to have an important impact on the development of molecularly defined immunotherapy currently being conducted with Fel d 1.

Investigations of the role of infection in allergic disease conducted elsewhere have focussed on viruses and atypical bacteria. Our studies on the protein antigens of the most common bacteria found in the respiratory tract of children, Haemophilus influenzae and Streptococcus pneumoniae show that more attention should be paid to these ever-present organism. Children who develop house dust mite allergy have a defect in the development of the protective IgG1 antibodies to both bacteria that precedes the development of allergy. In an unanticipated discovery it was shown that atopic and non-atopic children produce similar titres of IgE antibodies to protein antigens of these bacteria, which is lowest for children who develop asthma. This provides a new avenue to investigate the underlying differences in the immune system of children who become allergic and asthmatic. These studies are being undertaken with well-defined recombinant antigens that represent outer membrane proteins that are targets for protective immunity. A similar strategy has now been initiated with rhinovirus with the development of recombinant VP1 capsid antigens.

## Projects

### DEVELOPMENT OF ANTI-BACTERIAL IGG ANTIBODY IN HOUSE DUST MITE ALLERGIC CHILDREN

B. J. Hales, LY Chai, CE Elliot L. A. Hazell, W-A Smith, TK Heinrich, W. R. Thomas with M.M.H. Kusel, P. D. Sly and P. G. Holt from Cell Biology and Clinical Sciences

The development of IgG antibodies to bacteria that colonise the respiratory mucosa was studied by examining the responses the P4 and P6 antigens of the Haemophilus influenzae and the PspC and PspA antigens of Streptococcus pneumoniae. As shown by developmental deficiencies for antibodies to all the antigens, there was an overall defect for children who became house dust mite allergic. The defect was particularly evident at 2-3 years of age when responses first appeared but reduced titres to P6 however remained for 5 years. Since children typically do not show skin test reactivity or IgE anti-house dust mite allergen antibodies until they reach 4-5 years of age the defective IgG responses precedes allergic sensitisation. Depending on the antigen, the Th2-dependent IgG4 antibodies were found 30-50% of the children and the prevalences increased until 4 years of age after which, for H. influenzae, they fell significantly but only for the non-allergic subjects. This appears to be the antecedent of the persistent IgG4 responses found in some house dust mite allergic adults.

### THE PARADOXICAL IGE RESPONSES TO BACTERIAL ANTIGENS

B.J. Hales L. J. Pearce, L. A. Hazell, Y.L. Chai, C. E. Elliot and W. R. Thomas with P.G Holt, M.M.H. Kusel and PD Sly. Cell Biology and Clinical Sciences

IgE antibodies to the P4 and P6 antigens from Haemophilus influenzae (and PSP-C antigen of Streptococcus pneumoniae were found in 50-60% in sera from atopic and non-atopic teenagers with titres of about 1ng/ml to each antigen. The prevalence and titres of the responses to the different

antigens from different bacteria were highly correlated. There was no increase in atopic subjects and indeed within the atopic group the presence and titre of the anti-bacterial IgE was associated with a reduced risk for developing for developing asthma. The early infant cohort now shows that the antibodies were present by at least 5 years of age and like the older children this independent cohort showed that the presence of anti-bacterial IgE antibodies correlated with a reduced risk of asthma.

### RHINOVIRUS ANTIGENS

J Iwasaki, W. Smith, W. R. Thomas, C. E. Elliot, LY Chai, L. A. Hazell, B. J. Hales

The production of recombinant VP1 capsid protein from rhinovirus has been performed so that accurate measurements of isotype-specific antibody and T-cell responses can be made during the development and recovery from asthma exacerbations and to study associations of the antibodies with susceptibility to allergic and other respiratory disease. The VP1 proteins of members the type A, B and C families human rhinovirus are being made, Each has about 80% sequence identity within the family which is sufficient to measure cross reactive responses. The type C is a newly identified family that has been especially associated with lower respiratory tract infection and asthma. It has not been possible to cultivate the type C virus so the production of the recombinant polypeptide is the only avenue available to measure immune responses and conduct seroepidemiology. DNA encoding the VP1 antigens has been obtained by gene synthesis and expressed in E. coli. Antigens representing each of the serotypes have now been produced as soluble proteins and purified by multiple down-stream chromatographic procedures including size exclusion that has demonstrated the production of monomeric protein.

## FEL D 7 AND FEL D 8 ALLERGENS OF THE CAT

W. Smith, S. E. O'Neil, L. Y. Chai, L. A. Hazell, B. J. Hales, W. R. Thomas with S. Piboonpocanun and S. Thanyaratrisakul, Mahidol University, Bangkok

Fel d 7 is a salivary von Ebner gland protein similar to the major allergen of dogs and Fel d 8 is a protein from the cat mandibular gland similar to the surfactant-like latherin protein found in the skin and saliva of horses. Antibodies to the Fel d 7 allergen cross-reacted with the dog allergen for some sera and not for others. The allergen could be detected in high concentration in saliva. Both Fel d 7 and Fel d 8 bound IgE in the sera of over 40% of cat allergic subjects and for over 25% of cat-allergic subjects the titres to either Fel d 7 or Fel d 8 were both high and higher than that to Fel d 1. Along with previous observations with the lipocalin Fel d 4 the results show that the salivary gland proteins make a much bigger contribution to the IgE responses of cat-allergic subjects than expected, certainly the population of adults that develop rhinoconjunctivitis studied here.

## CD23 BINDING ASSAY IN CAT ALLERGY

L. Y. Chai, B. J. Hales, T. K. Heinrich, W. R. Thomas and B. J. Hales

The ability of complexes of IgE antibodies and allergen to bind to the low affinity CD23 IgE receptor was studied. The extracellular portion of the CD23 was produced as a recombinant polypeptide fused to a coiled coil leucine zipper that promotes the formation of trimers, similar to how they are found in nature. The CD23 was isolated by size exclusion chromatography as a trimer and coated onto microtitre wells and used to capture IgE immune complexes produced by the incubation of allergen and sera from allergic subjects. The binding was read out with anti-IgE antibodies in a dissociation enhanced lanthanide fluoroimmunoassay (DELFI). Studies with the Fel d 1 allergen showed that the IgE binding was only detected when both the IgE antibody

and allergen were present and was not found when IgE was depleted by RBL cells displaying the high affinity IgE receptor. Three out four subjects with IgE antibody to Fel d 7 had positive results when Fel d 7 was used showing that the CD23 binding complexes can be detected to newly defined allergens and could provide a new test to assess their clinical importance.

## External Committees.

W. R. Thomas. International Allergen Nomenclature Committee

## PhD thesis

Sarah B See. Outer membrane protein immunity to *Pasteurella pneumotropica* and the interaction of allergy. University of Western Australia

## 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

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

Investigators: Graham Hall, Stephen Stick, Sarah Ranganathan (VIC), Catherine Gangell, Shannon Simpson and Karla Logie as part of the AREST CF collaboration ([www.arestcf.org](http://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. We hypothesise that infants with cystic fibrosis will demonstrate abnormal peripheral lung function manifested as altered lung parenchymal mechanics as assessed by the low-frequency forced oscillation technique (LFOT) and by ventilation inhomogeneities as determined using multiple breath washout (MBW). Further, we hypothesise that those infants with increased pulmonary inflammation will have

correspondingly poorer peripheral respiratory function. The goals of this study are to evaluate these established standardised, 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

Investigators: Graham Hall, Peter Franklin, Zoltan Hantos and Mark Tan with the Peel Child Health Study ([www.peelchildhealthstudy.com.au](http://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

In 2010 we continued our strong recruitment success. Since recruitment began for this project about 80% of eligible (non-smoking) pregnant women have agreed to participate. We have successfully introduced the broad-band forced oscillation technique (FOT) into our lung function protocol. The Broad band FOT is a modified methodology based on the usual high frequency FOT we have used for many years. The successful integration of this test will provide new insights into lung

function in young infants and the potential impact of prenatal air pollution on lung health in these infants.

Funded by NHMRC

## Long term outcomes following preterm birth

### CHARACTERISING RESPIRATORY HEALTH OF YOUNG CHILDREN BORN PRETERM

Investigators: Graham Hall, Maureen Verheggen, Andrew Wilson, Stephen Stick, Jane Pillow

Advances in neonatal care have resulted in the survival of increasingly premature infants and changed the clinical presentation of bronchopulmonary dysplasia (BPD). The long-term respiratory outlook for young children born premature is not known. We aimed to characterize the lung function of young children born preterm in the surfactant era, who are now aged between 4 and 7 years by measuring lung function using Forced Oscillation Technique, Multiple Breath Washout, Diffusing Capacity, and Spirometry. We found children born preterm have worse lung function than healthy controls and that lung function worsened with increasing severity of disease. Symptom prevalence was similar in preterm children irrespective of BPD status. These results suggest that children born preterm have distal lung abnormalities which are more severe and sensitive to respiratory symptoms in those with BPD.

Funded by: Princess Margaret Hospital Foundation

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

Investigators: Graham Hall, Andrew Wilson, Jane Pillow, Andrew Maiorana, Shannon Simpson, Karla Logie and James Gibbons.

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. The aims of this project are to

- obtain novel information regarding lung structure in preterm children with and without a history of new bronchopulmonary dysplasia BPD using HRCT scanning of the chest.
- assess peripheral lung function using tests sensitive to the pathophysiological changes encountered in children with BPD
- determine the response to a maximal cardiopulmonary exercise test (CPET) in children with and without BPD.
- assess the importance of the relative effects of prematurity, neonatal lung disease and other perinatal factors on alterations in lung structure, function and respiratory morbidity.

Key findings in 2010 were that

- 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 BPD exhibited reduced gas transfer that was explained by a reduction in respiratory membrane diffusion and not pulmonary capillary blood volume.

Funded by NHMRC, Raine Foundation and Princess Margaret Hospital Foundation

## Asthma

### CHARACTERISING OBJECTIVE LUNG FUNCTION IN YOUNG CHILDREN WITH RECURRENT WHEEZE

Investigators: Graham Hall, Andrew Wilson, Stephen Stick, Shannon Simpson, Afaf Al Bloushi

Summary: Asthma results in episodic wheezing and is associated with cough and shortness of breath. In the majority of cases of persistent asthma, symptoms begin in early life with longitudinal studies suggesting that ~40% of children who wheeze in the first 3 years of life were still wheezing at 6 years. Patterns of wheeze prevalence and lung function are established by 6 years and do not change significantly by age 16. The pre-school years are therefore the time in which the most important alterations in lung function develop in susceptible individuals. In most asthmatics airway obstruction and its reversibility are quantified using spirometry. However spirometry requires considerable patient coordination and is not feasible for widespread use in young children. Lung function techniques, such as the forced oscillation technique (FOT) do not require active cooperation and are ideal for use in young children. The use of these techniques to assess lung function in young children with recurrent wheeze may have major implications for our understanding of asthma pathophysiology in this age group. This study is investigating

the influence of respiratory history and symptoms on lung function and bronchodilator responsiveness (BDR) in young children using the FOT and MBW techniques.

## Staff and Students

### HEAD OF GROUP

Graham L. HALL BAppSci, PhD, CRFS, FANZSRS  
Associate 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

Shannon Simpson PhD  
Andrew Wilson Paediatric Respiratory Physician

### POSTGRADUATE STUDENTS

Karla M Logie BSc(Hons) PhD Candidate  
Mark Tan BSc(Hons) PhD Candidate  
Maureen Verheggen BSc Masters Candidate  
Afaf Al Bloushi BSc Masters Candidate

## Awards

Graham Hall Fellow, Australian and New Zealand Society of  
Respiratory Science

## External Committees

### INTERNATIONAL

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

Graham Hall. European Respiratory Society Global Lung  
Initiative Task Force: Co-Chair (2008 - )

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

Graham Hall. European Respiratory Society Annual Congress  
Paediatric Respiratory Physiology Abstract review committee

### NATIONAL

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

Graham Hall. Thoracic Society of Australia and New Zealand  
Paediatric Special Interest Group: Convenor (2007 - )

Karla Logie - Thoracic Society of Australia and New Zealand  
and Australia and New Zealand Society of Respiratory Science  
WA branches (combined), Associates committee member.  
January – November 2010.

Karla Logie - Australia and New Zealand Society of  
Respiratory Scientists, Annual Scientific Meeting local  
organising committee member

### LOCAL

Graham Hall. Western Australian Health Department: Health  
Professions Strategic Reference Group (2007 - )

Graham Hall. Asthma Foundation of Western Australia Board  
member (2010 - )

## Invited Presentations

Graham Hall. Interpreting Spirometry in Children. American  
Thoracic Society Postgraduate Course on Case based:  
Pulmonary function test interpretation, New Orleans, May  
2010

Graham Hall. Does this wheezy child have asthma? Can  
diagnostic tests answer the question? American Thoracic  
Society Postgraduate Course on Case based: Pulmonary  
function test interpretation, New Orleans, May 2010

Graham Hall. Physiology Roadshow workshop. Joint  
Australian and New Zealand Society of Respiratory Science  
and Asia Pacific Society of Respirology, Ho Chi Min City August  
2010

Graham Hall. Preterm babies and lung health in later life: Do  
the lungs catch up? Women and Infant's Research Foundation:  
2010 Star Events. Perth September 2010

Karla M Logie. Expiratory flow dependence of exhaled breath  
temperature in children. European Respiratory Society Annual  
Scientific Meeting, Barcelona, September 2010.

## Overview

The Division of Population Sciences performs multidisciplinary research across a number of themes, including Nutrition, Developmental Health, Indigenous Health, Developmental Disorders and Mental Health.

The Division consists of almost 200 staff and students in multidisciplinary teams made up of epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists. Research is conducted collaboratively with partners in government as well as non-government organisations and community groups.

Divisional researchers use a range of research methods – both qualitative, involving participatory action research, focus groups and the exploration of the views and perceptions of community members in response to specific issues, and quantitative, such as analysis of complex linked databases with the view of identifying patterns and trends in child health.

The Division has a commitment to prevention and early intervention with a focus on assisting our government partners in finding solutions to issues identified for Western Australia's children and their families. 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.

## Highlights for 2010

In January, researchers within the Nutrition theme reported on research showing that children who are breastfed for longer than six months have a lower risk of mental health problems as they enter their teen years. The research found that breastfeeding for a longer duration appears to have significant benefits for the mental health of the child into adolescence. The research team analysed data from the Raine Study, which recruited 2900 pregnant women during 1989-1991 and have studied their children at various points to adulthood. Just over half were breastfed for six months or longer, 38% percent were breastfed for less than six months, eleven percent were not breastfed. The participants underwent a mental health assessment when they were 2, 5, 8, 10, and 14 years old. At each of the assessments, the research team found a link between breastfeeding duration and behaviour. For each additional month of breastfeeding, the behaviour score improved. This remained valid after adjustment for socio-economic, social and other factors impacting on parenting.

In February 2010, the Collaboration for Applied Research and Evaluation within the Division reported the results of a small scoping study on ADHD, concluding that a more comprehensive study is needed on the long term effects of ADHD medication such as Ritalin and dexamphetamine. The scoping study used data from the long term Raine Study and was funded by the Health Department of WA. While there were only 131 participants in the Raine Study who had ADHD (less than 5 per cent), the results did throw up some interesting findings that warrant further investigation. The data revealed that at age 13, children with ADHD on stimulant medication did not have significantly improved levels of depression, self perception or social functioning when compared with children with ADHD who were not taking medication. They were also more likely to be rated by their teacher as performing below their age level at school. What is still unclear however is

whether this is due to the effects of the drugs or whether it is due to differences in the underlying severity of ADHD symptoms between medicated and non-medicated groups. The study also suggested that there may be a small long-term effect of stimulant medication on blood pressure above and beyond the well documented short-term effects. While these differences were small, the research team said that this finding reinforces that doctors should closely monitor a child's cardiovascular function if treating with stimulant medication. The results of the scoping study did not allow conclusions to be drawn because of its significant limitations including the small number of cases. However it did reveal the need for a much more comprehensive long-term study to properly assess the benefits and risks of long term stimulant medication.

In May, Divisional researchers released the results of a study that found a link between children with larger head measurements in-utero and a subsequent diagnosis of Autism Spectrum Disorder (ASD) as toddlers. Fourteen children from the Raine Study who had been diagnosed with an Autism Spectrum condition were included in the study. The research team examined measures of prenatal growth taken from these children during their mothers' pregnancy, and compared these with 56 children who did not develop autism. The results showed that the children with largest head circumference measurements at 18 weeks gestation were at increased risk of Autism Spectrum Disorder. The study concluded that enlarged fetal head circumference relative to body size may be a risk marker for ASD. Due to the sample size, our researchers stress that these findings need to be replicated by other researchers. However, they may provide insights into the mechanisms underlying atypical brain development in ASD.

In June, researchers within the Division were awarded a prestigious Australian Research Council Linkage Grant to examine child, family and community factors affecting child development. The grant, worth more than two million dollars over five years, provides further funding for the successful

Developmental Pathways Project. This project involves the linkage of data held by eleven state government departments to get a broad picture of the factors affecting children's lives in Western Australia. The grant will enable Divisional researchers to analyze administrative information in ways that lead to real understanding about problems such as reasons behind an increase in child maltreatment and juvenile crime and point to mechanisms to address these issues.

In July, researchers within the Division reassured pregnant mums that relatively common stressful events during pregnancy do not have a long term impact on a child's language development. Previous research has linked maternal stress during pregnancy to behavioural and emotional problems in children. This is the first study to specifically address the effect of maternal stress during pregnancy on children's language ability. The language ability of 1309 children was assessed in middle childhood, between 9 and 11 years of age, with data for this research coming from the Raine Study. The research showed that relatively common stressful events experienced during pregnancy, such as financial or relationship difficulties, were not detrimental to the child's language ability at 10 years of age. The study found that the largest contribution to language development was the amount of time parents spent reading to their child during the first three years of life.

Also in July, the Division was awarded a prestigious Centres of Research Excellence Award. This award allows the Division to tackle the tough issue of why many programs have failed to deliver improved health for Aboriginal people. The National Health and Medical Research Council's Centre of Research Excellence Grant 'From marginalised to empowered: transformative methods for Aboriginal health and wellbeing' will provide \$2.5 million funding over five years. This innovative research program will generate vital information to address the issue of why the majority of health and social services have failed to bring about any significant improvements in the health and wellbeing of Aboriginal

people.

This research program will be led by Aboriginal researchers and will focus on the disparity between Aboriginal communities to identify why some programs and services are more effective than others.

Also in July, a study again using Raine data found an association between ADHD and a 'Western-style' diet in adolescents. Divisional researchers examined the dietary patterns of 1800 and classified diets into 'Healthy' or 'Western' patterns. The results revealed that a diet high in the Western pattern of foods was associated with more than double the risk of having an ADHD diagnosis compared with a diet low in the Western pattern, after adjusting for numerous other social and family influences. The study looked at the dietary patterns amongst the adolescents and compared the diet information against whether or not the adolescent had received a diagnosis of ADHD by the age of 14 years. A "healthy" pattern is a diet high in fresh fruit and vegetables, whole grains and fish. It tends to be higher in omega-3 fatty acids, folate and fibre. A "Western" pattern is a diet with a trend towards takeaway foods, confectionery, processed, fried and refined foods. These diets tend to be higher in total fat, saturated fat, refined sugar and sodium. The results suggest that a Western dietary pattern may indicate the adolescent has a less optimal fatty acid profile, whereas a diet higher in omega-3 fatty acids is thought to hold benefits for mental health and optimal brain function. Further to this, it may also be that the Western dietary pattern doesn't provide enough essential micronutrients that are needed for brain function, particularly attention and concentration, or that a Western diet might contain more colours, flavours and additives that have been linked to an increase in ADHD symptoms. It may also be that impulsivity, which is a characteristic of ADHD, leads to poor dietary choices such as quick snacks when hungry. This study suggests that while diet may be implicated in ADHD, more research is needed to determine the nature of the relationship.

In August, results of a study looking at child abuse found that most cases of child abuse or neglect that are identified in hospital are later substantiated. The study is the first in Australia to cross match anonymised hospital and child protection records. The results show that hospital protocols for reporting child maltreatment were working. The study used anonymised, record-linked child protection and hospital morbidity data to investigate public and private hospital admissions for children aged 0–17 years in Western Australia between 1 January 1990 and 31 December 2005 and their contact with the Department of Child Protection (DCP). The results showed that 90% of children admitted to hospital where concerns of maltreatment were identified had contact with the DCP. More than 80% of these children were notified to the DCP with a specific allegation and 68 % had substantiated allegations. The study confirms that most children suspected during a hospital admission of having been abused were notified to child protection agencies and most of these cases were substantiated. Specific injuries and conditions were associated with children who had greater contact with the DCP, included retinal haemorrhage, rib fractures, multiple injuries and malnourishment. The introduction of interdepartmental protocols to notify the DCP of all positive cases of sexually transmitted infections in children under the age of 14 means children who might previously have remained at risk of abuse are now successfully being identified. These results reinforced the important role that hospitals play in identifying children at risk of being abused so the cycle of abuse can be broken.

In October, Divisional researchers reported that women who drink heavily in the first trimester of pregnancy are four times more likely to have a child with certain types of birth defects. Heavy drinking is classified as more than seven standard drinks in a week. A standard drink is just 100ml of wine. The analysis was based on data drawn from a randomly selected cohort of more than 4700 non-Indigenous women who gave birth in WA between 1995 and 1997. This study reinforced

the need for health professionals to discuss alcohol use with women who are pregnant or of childbearing age. Nearly half of the pregnancies in the group of women in this study were unplanned which means heavy exposure can happen before a woman is aware she is pregnant. This means that prevention strategies will need to target not only pregnant women but also drinking at harmful levels and unplanned pregnancies among all women of child bearing age. The analysis showed no link between low alcohol exposure in pregnancy and birth defects.

Also in October, research led by the Head of the Division, Professor Stephen Zubrick concluded that children's development and wellbeing are under threat because their parents are fearful of strangers. The research involved a review of the evidence of parental anxiety as a barrier to children's physical activity such as walking or cycling to school and playing at parks. The evidence shows there have been substantial changes in Australian family life linked to work, employment, the extension of the lifespan, the lowering of the age-range for early childhood education and the need for care outside of the home. These factors, and changes to daily activity and routine, impart clear restrictions on where children can be left unsupervised, who can supervise them, the rules for transferring duty of care, and general tolerance for children having a 'free range' of independent mobility. The review found that parents often have distorted perceptions of 'stranger danger'. Such fear can curtail children's freedoms and physical activity. The research found that the negative impacts of parental fear and the resulting 'cottonwool' kids are increasingly being recognised as having adverse impacts on children, including less active lifestyles and increasing obesity levels. It appears that children are missing out on opportunities to develop important life skills that can be learnt through independent play and being allowed to move around within their neighbourhoods. The researchers recommended strategies in building social cohesion; creating environments to promote active engagement; transport initiatives to

promote walking and cycling; and empowering parents to be less fearful.

In November, Divisional researchers found that fertility rates increased following the introduction of the Federal government's "Baby Bonus" payments. While fertility rates went up across the board between 2004 and 2006, the most significant increases were among women from the highest socio-economic areas. The results of the study contradict the popular perception that the payments would increase pregnancies in teenagers and disadvantaged groups. The study showed that pattern of births in Western Australia changed after the introduction of the baby bonus payments, most particularly among women living in high socio-economic areas who previously had the lowest birth rates. These results suggest a positive change in perception about the value of parenting, awareness of declining fertility with age and a growing debate in our community of the need to balance career and family roles. The women contributing most to the increase were aged 20 to 29 years, and primarily living in areas of highest socioeconomic advantage characterised by a higher proportion of individuals with higher educational qualifications or in highly skilled occupations. These results have urgent implications for maternal and child health services. With more babies being born there is a need for more child health nurses, more schools and more early childhood professionals to support families.

In December, the Head of Nutrition research within the Division was named in the Nation's top ten health and medical researchers for 2010. Associate Professor Wendy Oddy's research investigating the links between child nutrition and physical and mental health was recognised at the National Health and Medical Research Council's Excellence Awards in Canberra. The awards were presented to the top 10 of almost 5,000 researchers nationally who applied for NHMRC funding this year.

Finally, also in December, results of a study using Raine data

found that children who are mainly breastfed for the first six months (or longer) score significantly higher academically at 10 years of age, especially boys. Academic data were collected for 1,038 eligible children at 10 years of age. After adjusting for gender, family income, and maternal verbal interaction, boys were found to have improved academic scores in maths, reading and spelling if they were breastfed for six months or longer. There was a small benefit for reading in girls. This study provides more evidence of the benefits of breastfeeding for six months or longer. There could be a number of ways that breastfeeding may boost academic achievement including vital nutrients in breast milk that support brain development, particularly in terms of long-chain fatty acids. Breastfeeding also has a positive effect on the mother-child relationship, thereby facilitating bonding, interaction and indirectly, cognitive growth. This study demonstrates the need for the community to provide more help and support for women to enable them to successfully breastfeed.

## Consumer and Community Participation in Population Health Research

In 2010, the Division of Population Sciences saw a significant increase in senior level support to enhance consumer and community participation in Divisional activities. Professor Steve Zubrick met with the Institute's Consumer and Community Advisory Council regarding the development of minimum standards for consumer and community participation for all research projects in the NHMRC Program Grant and the ARC Developmental Pathways Project. This has resulted in a range of outcomes including:

- A meeting with community members of the Council to provide input into the minimum standards.
- Endorsement by senior staff of a range of strategies aimed at increasing participation.

- Workshops on developing plain language summaries for all projects which culminated in 7 researchers presenting their final summaries to two judges at a special 'master class' presentation.
- Training workshops for researchers on implementing participation activities in their research.
- Development of a process for ongoing discussion between the Consumer and Community Advisory Council and the Chief Investigators.

Other participation initiatives within the Division included:

- Research areas and projects such as Infectious Diseases, the Raine Study, Growth and Development Study, Rett Syndrome and Down Syndrome Transition Project have continued ongoing support and development of a wide-range of consumer and community participation initiatives in research projects.
- A project for the development of a screening and diagnostic instrument for Fetal Alcohol Spectrum Disorders in Australia (FASD Project) included community participation activities in all aspects of the project. The project steering group includes three community advocates who provide a community perspective to the project.
- Over 50 people attended two community conversations on Infectious Disease Research at the Institute and the FASD Project. Input from both of these seminars will be used for planning of future activities in both areas.
- 40 researchers, administrators and students attended two training workshops in October on implementing consumer and community participation in research. These workshops were held at the Institute and were facilitated by Anne McKenzie (Institute Consumer Advocate) and Bec Hanley (UK Consumer Advocate).
- Deborah Lehmann, Hannah Moore and Kirsten Alpers

(Infectious Disease Research Group) were the recipients of the 2010 Consumer and Community Participation Award. The award acknowledges their ongoing commitment to supporting the Community Reference Group and a wide variety of community activities within the research group.

The Division of Population Sciences continues to support and demonstrate leadership in consumer and community participation in many of its activities. The new initiatives undertaken in collaboration with the Consumer and Community Advisory Council and the Chief Investigators of the NHMRC Program Grant and ARC Developmental Pathways Project in 2010 are contributing to the development of best practice examples of consumer and community participation in both the national and international arenas.

## Aboriginal Health Research

### ABORIGINAL COLLABORATION COUNCIL ADVISING ON RESEARCH AND EVALUATION

Roz Walker, Patricia Walsh.

The Aboriginal Collaborative Council Advising on Research and Evaluation (ACCARE) has a primary goal of facilitating, translating and applying research findings into policy and practice. ACCARE's Terms of Reference include providing a forum for statewide representation and consultation by Aboriginal government and non-government agencies and service deliverers on whole of life Aboriginal issues; and informing outputs of activities and work plans of Aboriginal research conducted by the Telethon Institute for Child Health Research (TICHR) and partnering agencies. The Council also provides advice on and support for effective communication and dissemination of information on Aboriginal research and research findings relevant to policy and service delivery for Aboriginal children and families/communities. A key role is to provide a peak body for advocacy and discussions for

Aboriginal research at TICHR in collaboration with appropriate external organizations and to actively identify, support and foster new research opportunities for Aboriginal research and Aboriginal researchers. This also includes monitoring the effective implementation of Aboriginal research at TICHR using a range of existing and new mechanisms and agreed criteria and priorities.

Professor Rhonda Marriot, the Chair of ACCARE is also a Director on the TICHR Board. ACCARE is a committee of the Board providing input into research. Importantly ACCARE performs an advisory council function for Kulunga Research Network and is a conduit to ensure Aboriginal community research priorities are conveyed to Kulunga/TICHR and key relevant external bodies such as the Indigenous Implementation Board.

Key activities in 2010 include establishing a sub-committee to develop a Winter School Training Program with an aim to building research capacity in Aboriginal Health Research; and raising the profile of ACCARE. This has been achieved through a range of activities including: developing a Vision and Mission Statement; creating a Webpage detailing the role of ACCARE; and all Aboriginal Health Research milestones achieved at TICHR commencing in 1999 to present day, and maintaining a display board to highlight Aboriginal Health Research at TICHR; publishing articles in the TICHR Annual Report and the TICHR news, the internal newsletter for staff and students. In the past 6 months the circulation list to Aboriginal stakeholders has been extended.

ACCARE meets for a half day 7-8 times a year. Four meetings were held between July and December 2010 to provide advice and support to TICHR, Department of Health WA (DOH) and the Women's and Newborn Health Network (WNHN) projects involving Aboriginal research, including the new National Health and Medical Research Council (NHMRC) Centre for Research Excellence on Aboriginal Health and Wellbeing; and to advise and disseminate information on several Aboriginal

health projects identified as priority areas in closing the gap in Aboriginal health outcomes. A planning retreat was held in November to review progress to date and undertake planning for 2011.

Funders of the project: Western Australian Department of Health

## KULUNGA RESEARCH NETWORK

In addition to progressing all current projects the focus in 2010 has been on building new relationships. Several of the team members employed for specific projects moved on once their projects were successfully completed.

Dr Kate Riddell - was appointed to a senior policy position at the Office of Multicultural Affairs following the completion of the Rio Tinto Aboriginal Health Partnership – Strong Foundations, Sustainable Futures project.

Francine Eades moved to the Eastern States with her family.

Josephine Maxted was appointed to a senior position at the Department of Corrective Services.

Associate Professor Roz Walker has continued to work with Kulunga as a research consultant to complete the publication of the Australian Council for Education Research (ACER) Mental Health Textbook, *Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice*.

Carrington Shepherd also works with Kulunga on requests for the WA Aboriginal Child Health Survey data.

Dr Clair Scrine returned from maternity leave in July and is working part-time as a Senior Research Officer.

Two new team members joined Kulunga in the latter part of the year to support the new strategic direction.

Rose Murray - Rose is a Nyangumarta woman whose early education was in Victoria and as an adult in Western Australia.

Rose has a Diploma of Teaching (Primary) Western Australian College of Advanced Education and an Advanced Certificate in Aboriginal Health Promotion from Combined Universities Centre for Rural Health (CURCH) /Curtin University. Rose was on the first national Council for Aboriginal Reconciliation and is a life member of Country Arts WA.

Previously Rose worked all over Australia with Fred Hollows and the National Trachoma and Eye Health Program. Rose has been on many local, state and national committees and has also researched Aboriginal/police relations, family history and women's issues. She was a founding committee member of Wirrakamaya Aboriginal Health Service in Port Hedland. Rose has worked extensively in Aboriginal community based organizations. More recently, Rose was working at the Geraldton- Greenough Regional Library in the Heritage Services section.

Fred Stacey BA. Fred has a Bachelor of Arts in Social Science with a double major in Sociology and a major in Public Administration. He has a strong background in public policy and has held senior positions in government both in WA and the NT. In the NT he was a member (representing the Department of Health and Families) of the senior officers work group to the NT Research and Innovations Board and was also involved in the work program at Charles Darwin University, the Menzies School of Health Research and the Cooperative Research Centre for Aboriginal Health. More recently, Fred has held positions providing policy advice to the Board of the Aboriginal Health Council of Western Australia and change management consultancy at Danila Dilba Health Service (Darwin) and Derbarl Yerrigan Health Service – including development of the GP Super Clinics in Palmerston (NT) and Midland.

## INDIGENOUS MENTAL HEALTH TEXTBOOK

Nola Purdie, Roz Walker, Pat Dudgeon.

This project was a collaboration between the Australian Council for Education Research (ACER), Kulunga Research Network and Telethon Institute for Child Health Research. Assoc. Prof. Roz Walker is an editor for 'Working Together - Aboriginal and Torres Strait Islander Mental Health and Wellbeing, Principles and Practices', with Dr Nola Purdie, ACER and Assoc. Prof. Pat Dudgeon, for Kulunga. The book which was completed in December 2009 explores culturally appropriate approaches to assessment and interventions for Aboriginal and Torres Strait Islander social and emotional wellbeing and mental health issues. Thirty-eight Indigenous and non-Indigenous clinicians, cultural and educational experts from around Australia contributed to 21 chapters in the book.

Several Institute research staff contributed to the book. Prof. Steve Zubrick co-authored two chapters with Assoc. Prof. Roz Walker and colleagues – the policy context of Indigenous mental health and wellbeing and the social determinants influencing Aboriginal and Torres Strait Social and Emotional Wellbeing. Assoc. Prof. Pat Dudgeon, Dr Michael Wright and Assoc. Prof. Ted Wilkes contributed to chapters on social and cultural contexts of Indigenous Mental Health and substance use respectively. Prof. Sven Silburn completed a Chapter on Preventing Suicide in Indigenous populations. A PDF version was completed in 2009 and hardcopies were published March 2010.

Funders of the project: Department of Health and Ageing, Office of Aboriginal and Torres Strait Islander Health, Canberra.

## THE COMMUNICATION, DISSEMINATION AND EVALUATION OF WORKING TOGETHER ABORIGINAL AND TORRES STRAIT ISLANDER MENTAL HEALTH AND WELLBEING PRINCIPLES AND PRACTICE

Roz Walker, Pat Dudgeon.

This project which commenced in July 2010 involves both the widespread dissemination of the book 'Working Together' to universities and training colleges and the health and social services sector throughout Australia and the evaluation readability and usefulness of the text for these key stakeholders.

The book, which is available free of charge, is intended to assist the health workforce to contribute to the State and Australian Government's commitment to improve the mental health and wellbeing of Aboriginal and Torres Strait Islander peoples. It offers new approaches to Indigenous mental health that simultaneously acknowledge the importance of cultural identity and resilience that exists as well as the pervasive effects of racism, and the disempowerment of colonisation and assimilationist policies. The book will enable practitioners to understand the historical and contemporary influences and social determinants that impact on the social and emotional wellbeing of Indigenous Australians and the interrelationship with mental health policy directions. It will greatly assist all students of medicine, psychology, allied health and education when working with Indigenous Australians.

Over 45,000 hard copies of the book were printed and more than 15,000 of these were distributed by December 2010. The book is also available on line through the Kulunga Research Network at the Telethon Institute for Child Health Research. An online evaluation will be conducted during the first semester of 2011 and reported by July.

Funders of the project: Department of Health and Ageing, Office of Aboriginal and Torres Strait Islander Health, Canberra.

## EXAMINING THE CRITICAL FACTORS IN ABORIGINAL NON-SMOKING

Clair Scrine, Rose Murray.

Kulunga and the Cancer Council of WA commenced a collaborative research project in 2010 to explore the factors contributing to Aboriginal smokers successfully quitting.

This project builds on an earlier project that was undertaken for the Cancer Council (WA) that examined the impact of the 'Make Smoking History' advertising campaign among Aboriginal smokers in Western Australia.

The current project seeks to help better understand the factors that play a role in Aboriginal people effectively quitting smoking or avoiding starting. The research is intended to assist the Cancer Council (WA) in its development of appropriate and effective campaign materials and educational resources for use with Aboriginal people.

Funders of the project: The Cancer Council WA.

## RIO TINTO ABORIGINAL HEALTH PARTNERSHIP – STRONG FOUNDATIONS, SUSTAINABLE FUTURES

Glenn Pearson, Kate Riddell, Josephine Maxted, Clair Scrine, Rose Murray.

The Rio Tinto Aboriginal Health Partnership (RTAHP) is a collaboration between the Kulunga Research Network, the Telethon Institute for Child Health Research and Rio Tinto. It commenced in July 2008 and officially concluded in August 2010. The Partnership has sought to bring about improvements in the area of Aboriginal child and maternal health through the Strong Foundations, Sustainable Futures (SFSF) project, more specifically through four core components designed to address some of the training, development and support needs of Aboriginal Health Workers in the East Kimberley, Pilbara, and South Metropolitan area of Perth.

The SFSF project has sought to address the need for capacity building initiatives and on-site skills training for Aboriginal Health Workers to support their career pathways and ensure they feel empowered, capable and confident. The Partnership and Project have sought to fulfill a number of objectives related to this need by delivering training, a health-worker resource manual, and awarding scholarships to Aboriginal Health Worker students studying at registered training organisations.

The project team completed the following key deliverables:

- Development, production and delivery of the Start Stronger, Live Longer health-worker resource manual for Aboriginal Health Workers. The conceptual basis of the resource is 'health for life,' emphasizing the importance of a good start in life as foundational to a longer, healthier life. It focuses on seven key themes: Maternal Health and Wellbeing; Infant and Child (0-5) Wellbeing and Development; Adolescent Health and Wellbeing; Mental Health and Wellbeing; Nutrition and a Healthy Lifestyle; Smoking, Alcohol and other Drugs; and How to Do Health Promotion and Re-search.
- Delivery of training and resource manual roll-out workshops in the key regions. Commencing on March 17 2010, these workshops consisted of expert training around key themes addressed in the resource manual, as well as guiding Health Workers through the manual and demonstrating how the resource can be used in health education and promotion activities. Ongoing support to health Workers and Aboriginal Medical Services and distribution of the resource manuals has continued.
- Start Stronger, Live Longer National Health Worker Symposium. This event was held on 8 and 9 June 2010 at the University of Western Australia University Club. The symposium program was organized around the themes of the resource manual, and included key note speeches, plenaries and breakout sessions. The symposium

was well attended by representatives of a range of organisations across the country, and provided Aboriginal Health Workers the opportunity to learn, up-skill and network with experts and colleagues.

Funders of the project: Rio Tinto.

## EVALUATION OF THE MICHAEL LESLIE PILBARA PERFORMING ARTS PROGRAM

Kate Riddell, Clair Scrine, Rose Murray.

The evaluation seeks to assess the Michael Leslie Pilbara Performing Arts Program against its core objectives of enabling improved educational attainment, self-esteem and aspiration in its Aboriginal and non-Aboriginal students. It seeks to develop a greater understanding of the impact and outcomes of the program specifically, and from this draw conclusions about the efficacy of arts-based youth programs more generally on students and their learning and development.

Funders of the project: This project is funded by a Healthways Health Promotion Research Starter Grant.

## TREADING CAREFULLY: SOCIO POLITICAL IMPLICATIONS OF GENETIC RESEARCH IN ABORIGINAL AND TORRES STRAIT ISLANDER COMMUNITIES

Emma Kowal, Glenn Pearson, Jenifer Blackwell, Roz Walker.

Human genetic research promises to deliver a range of health benefits to the population. Where this research involves Indigenous communities, many sensitive issues are raised. Indigenous peoples around the world have expressed concern about a lack of benefit to their communities; a diversion of attention from non-genetic causes of health disparities; a reinforcement of 'victim-blaming'; and possible misuse of tissue samples. These issues have not been studied in an Australian context. As there is an imminent expansion of

genetic research with Indigenous people in Western Australia, both non-Indigenous genetic researchers and Indigenous researchers have expressed the need to rectify this.

This project aims to identify the ethical, socio-political and philosophical issues raised by genetic research with Indigenous communities, and promote informed debate on these issues. It has five overlapping phases: literature review, community consultation, participant-observation, interviews, and analysis and feedback. There will be three groups of participants: genetic researchers, Indigenous community leaders, and Indigenous people who are participating in genetic research projects.

This project commenced as a post doctoral research project (has subsequently received an NHMRC grant) and is being led by Dr Emma Kowal from the University of Melbourne.

## IMPLEMENTATION AND EVALUATION OF THE AUSTRALIA EARLY DEVELOPMENT INDEX (INDIGENOUS ADAPTATION) IN THE WESTERN DESERT COMMUNITIES BHP BILLITON 2009-2014

Roz Walker, Clair Scrine, Rose Murray.

The Telethon Institute for Child Health Research and BHP BIO have entered into a new partnership to support and evaluate the BHP Billiton Iron Ore's (BHPBIO's) Community Investment Program 2009-2014 which is focused on creating long term benefits for the Aboriginal communities in the Western Desert. The Community Investment Program 2009-2014 maternal and child health initiative for the Western Desert communities is largely based on the Australian Early Development Index (AEDI) Pilbara Community 2007 results from the 'Starting on Track' AEDI implementation project. The initiative collected information across five developmental domains which measure early child development and school readiness. These domains include: Physical health and well-being; Social competence; Emotional maturity; Language

and cognitive development; and, Communication skills and general knowledge. The AEDI 2007 and I-AEDI 2008 results for the Jigalong, Punmu, Parngurr and Koonawarrji communities confirm the critical need for a strategic focus on programs to improve early years outcomes for children 0-5 years as well as a reorientation of services to improve maternal health and early years development outcomes across all development domains. The 2008 I-AEDI results provide the baseline to measure improvements in early years development in Aboriginal in these communities over time.

The research project will use three key measures on an annual basis for five years to guide and evaluate BHPBIO's maternal and early child development initiative: 1) the implementation of the Australian Early Development Index (AEDI) (which now incorporates Indigenous elements); 2) the 0-5 years Aboriginal Health Schedule (Department of Health) recently reviewed by TICHK; and, 3) existing maternal health indicators developed for the Overcoming Indigenous Disadvantage COAG initiatives. Together these measures will provide a robust evidence base to inform and evaluate the new BHPBIO Aboriginal early child and maternal health initiative in Jigalong and other Western Desert communities. The project uses a community based action research process to implement and disseminate the AEDI results and trial the 0-5 Child Health Schedule to build community capacity and sustainability and improve maternal health and child development, education, health and wellbeing outcomes over the next five years.

These results will be used to inform BHPBIO of the effectiveness of various existing early years

interventions and strategies as well as signalling those that are less successful. The results will

confirm whether and in what ways there is a need for the reorientation of program support or strategic intervention in particular communities. The collection of data on an annual basis for 4, 5 and 6 year olds will provide school based profiles which will enable the schools to gauge shifts in developmental

domains over time. This is a unique opportunity to provide fine grained monitoring and evaluation of the Community Investment Program 2009-2014.

Funder of the project: BHP Billiton Iron Ore Community Investment Program.

The following Aboriginal Research projects were conducted through the Collaboration and Applied Research Evaluation (CARE):

#### **IMPROVED COMMUNICATION AND INFORMED DECISION MAKING BY ABORIGINAL FAMILIES: PRENATAL DIAGNOSIS, NEONATAL CARE, AND END OF LIFE DECISIONS**

Roz Walker.

This qualitative research project aimed to identify ways in which King Edward Memorial Hospital and Princess Margaret Hospital can improve communication between their staff, relevant health professionals and Aboriginal families to assist with the decision making surrounding serious illness for babies and end of life decisions in the perinatal and neonatal period. The research outcome for this project was the development of a more effective and culturally appropriate practices and procedures to improve communication between health care professionals and Aboriginal families around health care and end of life decisions prenatal and neonatal periods.

This project has produced a draft resource kit to assist staff at KEMH (and other relevant hospitals) in understanding and working with an Aboriginal family to assist them to make decisions regarding their unborn or newborn child (or children). In addition, a culturally appropriate resource kit has been produced to assist Aboriginal and Torres Strait Islander families experiencing the death or dying of a child in making health care decisions for their child which take account of their family and community context.

The final report on the research is currently being finalized and will include a comprehensive literature review, research findings and recommendations. The most significant finding is the need for cultural competence at system, organizational and individual practitioner levels.

Funders of the project: Western Australian Department of Health (a CARE project).

#### **EVALUATION OF THE CULTURAL COMPETENCE AUDIT TOOLKIT**

Roz Walker with the Women's and Newborn Health Network.

Two studies on antenatal and maternal health services for Aboriginal women undertaken by TICHR on behalf of the Women's and Newborns' Health Network confirmed that Aboriginal people in Western Australia have the limited access to culturally responsive health and social services. An outcome of this research was the development of two tools: an Organisational and Cultural Competence Assessment Tool and an Individual Cultural Competence Assessment Tool; which were included as part of a comprehensive resource for practitioners to assist them in more effectively communicating with Aboriginal families in a health care setting such as a maternity hospital.

The aim of this study was to further develop, trial and evaluate the Organisational and Individual

Cultural Competence Assessment tools. In particular, the study aimed to evaluate:

- The usefulness and acceptability of the Individual Cultural Competence Assessment Tool in the promotion of critical self-reflection and self-reported changes in individual cultural competence.
- The usefulness and acceptability of the Organisational Cultural Competence Assessment Tool for management personnel in assessing the cultural competence of the organisation and its relevance to the organisation's

Continuous Quality Improvement (CQI) process and implementation of the Reconciliation Action Plan.

A literature search was undertaken in developing and refining the cultural competence tools. The

review focused specifically on cultural competence and associated terms in Australia and internationally. The Cultural Competence Assessment Tool was refined and provided to staff who agreed to participate in the study along with an evaluation questionnaire and additional resources. Small group discussions were held with senior staff at both King Edward Memorial Hospital (KEMH) and Princess Margaret Hospital for Children (PMH). Discussions were held with staff at a cultural awareness workshop to explore the notion of 'unpacking white privilege' and the relevance and usefulness of the reflective exercises within the Individual Cultural Competence Assessment Tool. In addition, a group of midwives, senior nurses and allied health staff at KEMH participated in the trial and evaluation of both the Individual and Organisational Cultural Competence Assessment Processes, and senior executive staff at KEMH and PMH participated in trialling the organisational tool. Several Health Department personnel also formed the trial sample group which totalled approximately 55 staff across the sector. Meetings with the Aboriginal Health Advisory and Action Council at PMH provided in-principle support for the trial as did the Aboriginal Collaboration Council for Research and Evaluation at TICHR.

The results showed that a significant number of hospital staff working with patients were unaware of the various guidelines and frameworks to support culturally responsive services. Many staff did not know whether their hospital had a Reconciliation Action Plan, and several were unaware of Aboriginal health policies. The overwhelming majority agreed that Individual Assessment Tool was easy to use and understand and the overall process was user friendly. The majority agreed that the assessment process provided clear

direction to realistic and appropriate actions and resources and that completing the Individual Assessment Tool improved their understanding of cultural competence and the relevant policies to ensure more culturally responsive services. Many stated that completing the tools also encouraged them to participate in cultural competence activities and strengthened their commitment to engage with activities which support organisational, professional and system level changes. All participants in senior positions agreed or strongly agreed that the Organisational Assessment Tool is relevant; is a means to embed cultural competence within the organisation; assists in the implementation of Reconciliation Action Plans; and supports hospital staff in developing their understanding and skills in a cost effective and non-threatening way.

The Cultural Competence Tools acknowledge the unique place of Aboriginal people, their traditional and colonial histories and contemporary social, political, cultural and economic circumstances that can impact on health outcomes. While these Tools were developed specifically with a focus on Aboriginal people, the framework and the engagement in critical self-reflection will enhance the capability of practitioners and other personnel to work more effectively with all culturally diverse groups. Given the widespread support for the implementation of cultural competence in the health sector the next steps involve identifying the strategies required for a state- and health sector-wide implementation.

Funders of the project: Western Australian Department of Health (a CARE project).

## EVALUATING THE HALLS CREEK COMMUNITY FAMILIES PROGRAM

Roz Walker, Valma Banks, Ailsa Munns.

'Yanan Ngurrangu Ngamayiu' is a home-visiting program for Aboriginal pregnant women and parents of young children 0-3 years old which commenced in 2008. Experienced Aboriginal

mothers and grandmothers are trained as community care workers to provide parents with support to improve, parental health behaviour and attitudes, and infant and child health outcomes through a range of culturally appropriate activities including home visiting. This project evaluation aims to assess whether and in what ways families and staff involved with the program believe that it has increased their level of self-empowerment, knowledge and understanding of the importance of parenting roles and improved their health and wellbeing through the collection of participant stories. It aims to understand the extent to which the program is empowering for mothers and community care workers; improving health and development outcomes for children; and, enhancing social networks and communication between health care professionals and Aboriginal mothers and their families.

A qualitative method was used to obtain Aboriginal mothers/carers and family program staff and relevant stakeholders perspectives regarding the value and effectiveness of the program. MSC stories were collected from staff participants and 12 families, and discussions and semi-structured interviews were completed with several key relevant stakeholders in Halls Creek. The information reveals different perspectives, expectations and understandings of Aboriginal women and their families, community care workers and other health professionals and local stakeholders. A preliminary analysis of the MSC stories provides examples of how participation in the HCCFP improves people's sense of empowerment, engagement with and access to health services and improvements in the health and social and emotional wellbeing of their children and families.

These stories highlight that program participants are encouraged and supported to: discuss their concerns about their roles, relationships, child development and other issues with community care workers and relevant others; further develop their relationship skills and community links; increase the quality and access to personal exchange opportunities; and, extend their social networks and quality of

communication with significant others. Some of the families have identified changes in beliefs about parenting roles and greater understanding of using different ways to manage their children's behaviours and 'the importance of good food and hygiene. Overall all of the stories suggest there is a positive program effect on maternal care.

Findings confirm the program is making a positive difference for families and increasing antenatal services linkages and outreach; the inclusion of male community care workers has also proved highly valuable by involving fathers and grandfathers in considering issues of nutrition, alcohol and depression and support for fathers. Elements including the integrated program implementation, monitoring and evaluation; ongoing onsite training and education are providing program participants and staff with valuable opportunities for learning and empowerment. Moreover, the participatory action, reflection review processes built into both the course delivery and evaluation have the potential to fill knowledge gaps around theories of empowerment and capacity building for individuals, families, communities, and organisations in cross-cultural contexts. The participatory evaluation was completed in July 2010 and the Final Report was completed in December 2010.

Funders of the project: Western Australian Department of Health (a CARE project).

## THE INDIGENOUS AUSTRALIAN EARLY DEVELOPMENT INDEX (I-AEDI) PROJECT

Sven Silburn, Sally Brinkman, Bonnie Moss, Anne Hanning; Roz Walker.

Initiated in 2007, the Indigenous Australian Early Development Index (Indigenous-AEDI) project adapted the widely used Australian Early Development Index (AEDI) to take into account Aboriginal cultural differences in the influences on child development. The study was overseen by a National

Indigenous AEDI Reference Group with input from Indigenous peak bodies and grass roots community organisations, parents, unions and government and non-government stakeholders throughout the project.

The first phase was completed in 2008 and third and final phases were completed in 2009. The adapted version of the AEDI was piloted in 2008 with Indigenous children from 49 schools in three sites around Western Australia— Armadale, Murchison Gascoyne and the Pilbara. In 2009 the study focused on communicating and disseminating the results in trial sites identifying and using local, culturally relevant and meaningful resources and processes. The study was extended to the Northern Territory.

Based on the findings of the study an adapted Checklist was integrated into national AEDI checklist in 2009 with the following modifications:

- The recommended use of Indigenous school personnel to work as cultural consultants with teachers in completing the AEDI checklists for Indigenous children.
- Modifications to the on-line teacher guide to provide additional information so that cultural considerations can be taken into account on certain checklist items.
- Additional checklist items of relevance to understanding the particular circumstances of Indigenous children. That may affect attendance and performance (cultural, sickness or other); use of home language, history of otitis media or hearing difficulties.

These modifications were included for all children in national data collection in 2009. The recommendations seek to strengthen recognition and appreciation of Indigenous cultural ways of understanding and promoting children's learning and adaptive behaviour by school and other early childhood personnel. The Indigenous Adaptation Study is an important step in ensuring not only the cultural accuracy of the AEDI, but also its effectiveness in empowering communities to enhance

the development of all children in their critical early years.

Existing AEDI community preparation materials and AEDI community reporting processes were reviewed at community forums and consultations and new strategies identified for dissemination of the findings and their translation into action by communities, government and non-government service providers. Templates for presenting AEDI findings using a variety of visual representations of data customised to local requirements and language were developed and trialed including icons and bar graphs to enhance lay understanding of scientific concepts. Laminated A3 flip-charts and posters describing the AEDI domains in a 'mindmap' with photos showing practical examples of children's behaviours and competencies were found to be particularly useful for engaging with parents and community stakeholders.

The study findings highlight the benefits of collaborative checklist completion by teachers and Indigenous cultural consultants as a valuable professional and personal development opportunity for both Indigenous and non-Indigenous school personnel. The findings confirm that the adapted AEDI can be reliably and effectively administered in conjunction with the existing AEDI process and provides a culturally equivalent community-level measure of overall early child development.

Dissemination methods are now being developed and trialed in the Northern Territory and Queensland and in the Pilbara Western Desert communities. Training packages are being developed to build capacity and enable communities across Australia to advocate for early childhood and work with the AEDI results locally.

A report on the findings of project is available on the AEDI website.

Silburn S, Brinkman S, Ferguson-Hill S, Styles I, Walker R, and Shepherd C. 2009 The Australian Early Development Index (AEDI) Indigenous Adaptation Study. Perth: Curtin University of

Technology and Telethon Institute for Child Health Research. [http://www.rch.org.au/aedi/about.cfm?doc\\_id=13283](http://www.rch.org.au/aedi/about.cfm?doc_id=13283)

Funders of the project: Funding through Shell Australia, Department of Education, Employment and Workplace Relations (Australian Government).

#### LOOKING FORWARD: IMPROVING MENTAL HEALTH SERVICE OUTCOMES FOR ABORIGINAL PEOPLE LIVING IN THE ARMADALE STATE HEALTH REGION

Michael Wright, Fiona Stanley.

This project is a partnership between Aboriginal families[1], 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 Armadale State Health Region. 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 culturally safe mental health framework that will be trialed and evaluated to determine whether this service delivery framework has made a difference to the delivery of mental health services to Aboriginal families living in the Armadale State Health region.

The methodology for the project is to conduct 12 community forums across the region. The forums will begin in March 2011 and it is expected that they will extend for a period of 12 months. The project is expected to be completed at the end of 2013.

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

## Birth Defects and Developmental Disorders

### FETAL ALCOHOL SPECTRUM DISORDERS: DEVELOPMENT OF A SCREENING AND DIAGNOSTIC INSTRUMENT FOR AUSTRALIA (FASD PROJECT)

Carol Bower & Elizabeth Elliott (lead investigators), Laura Bond & Heather Jones (project staff) and the Steering Group: Dr Lucinda Burns, Ms Maureen Carter, Ms Heather D'Antoine, Dr James Fitzpatrick, Assoc. Prof Jane Halliday, Ms Lorian Hayes, Dr Bill Kean, Assoc. Prof Jane Latimer, Ms Anne McKenzie, Ms Sue Miers AM, Dr Raewyn Mutch, Dr Colleen O'Leary, Ms Jan Payne, Dr Elizabeth Peadon, Ms Elizabeth Russell, Dr Amanda Wilkins.

This one-year project funded by the Commonwealth Department of Health and Ageing, is lead by Professors Carol Bower and Elizabeth Elliott (University of Sydney) and a multidisciplinary Steering Group. The aim of the project is to develop of a screening and diagnostic tool which can be used nationally to:

- Aid early recognition of Fetal Alcohol Spectrum Disorders;
- Improve access to health and education interventions and hence health and educational outcomes for babies, children or young people diagnosed with a Fetal Alcohol Spectrum Disorder; and
- Improve the quality of life for children and families affected by a Fetal Alcohol Spectrum Disorder

A systematic review of literature published worldwide (including government and other websites and reports) has been completed and, based on the information gleaned, statements for use in a Delphi survey are being constructed. The Delphi technique is a way of seeking opinion and gaining consensus from a range of people on a specific topic. In this case the topic is "the best way to screen and diagnose fetal alcohol spectrum disorders". Participants in the Delphi

process will include: doctors, nurses, clinical psychologists, social workers, occupational therapists and speech pathologists. In the Delphi process, participants will be asked to rate statements about Fetal Alcohol Spectrum Disorders on a scale of 1 – 5 (strongly agree to strongly disagree). After 2-3 rounds of reviewing and rating statements, we hope to reach a consensus view on what should be included in the screening-diagnosis instrument.

We have held one community workshop (and a second is planned) to discuss Fetal Alcohol Spectrum Disorders and engage women aged between 18 and 45 years in conversations about the type of testing they think would be appropriate when a health professional is screening for, or diagnosing Fetal Alcohol Spectrum Disorders in children. We will also seek women's opinions about appropriate language and questions to be used by health professionals when discussing the issue of alcohol use in pregnancy. This information will be used by the Steering Group when developing the screening and diagnostic instruments.

Funders of the project: Department of Health and Ageing; NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).

### PRENATAL ALCOHOL EXPOSURE AND BIRTH DEFECTS

Colleen O'Leary, Natasha Nassar, Jennifer Kurinczuk, Nicholas De Klerk, Elizabeth Geelhoed, Elizabeth Elliott, Carol Bower.

For this analysis we used data from a randomly selected, population-based cohort of 4714 non-indigenous women linked to WA Birth Defects Registry data. We classified birth defects as alcohol-related according to the Institute of Medicine (IOM) classification. We found that the prevalence of birth defects thus classified was low. Compared with abstinence, heavy alcohol exposure in the first trimester was associated with increased odds of these birth defects

(adjusted odds ratio: 4.6 [95% confidence interval: 1.5–14.3]). There was no association between low or moderate prenatal alcohol exposure and these birth defects.

Funders of the project: NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).

### PREGNANCY OUTCOMES FOLLOWING ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

Michele Hansen, Lyn Colvin, Beverly Petterson, Jennifer Kurinczuk, Nick de Klerk, Carol Bower.

Using record linkage, we are investigating the risk of birth defects in children conceived by assisted reproductive techniques (ART), compared with spontaneously conceived children. In particular, we are replicating an analysis conducted in a study from Victoria looking at blastogenic defects – those that occur very early in pregnancy (by 28 days post-conception). An increase in these birth defects in ART infants was found in the Victorian study, suggesting that events in the process of assisted conception at or around the time of implantation may be disturbing early embryo development.

We are now collaborating with researchers from the National Perinatal Statistics Unit in New South Wales to extend this study in order to examine inpatient hospital costs in the first 5 years of life for all children born in WA between 1994 and 2003. This study should allow us to estimate the potential savings in hospital costs if a 5% or 10% multiple gestation rate after ART is achieved.

Funders of the project: NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).

## PHARMACOVIGILANCE IN PREGNANCY USING POPULATION-BASED LINKED DATASETS

Lyn Colvin, Linda Slack-Smith, Fiona Stanley, Carol Bower.

Recent studies have reported links between prenatal exposure to the group of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) and increased risk of adverse pregnancy outcomes. Using data linkage of population-based health datasets from Western Australia and a national pharmaceutical claims dataset, we compared birth outcomes for women who were dispensed an SSRI in pregnancy (3,703 women) to all other women with a birth during the same period (93,265).

We found an increased risk of cardiovascular birth defects in the offspring of women dispensed an SSRI during the first trimester, and an increased risk of particular birth defects associated with specific SSRIs. Also, the women dispensed an SSRI were significantly more likely to give birth prematurely and their children were more likely to have a lower birth weight and shorter birth length.

Funders of the project: Australian Postgraduate Award (LC).

NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).

## THE INFLUENCE OF AMBIENT AIR POLLUTION FROM TRAFFIC EMISSIONS AND PREGNANCY OUTCOMES

Gavin Pereira, Angus Cook, Natasha Nassar, Carol Bower, Nick de Klerk, Phillip Weinstein.

Two papers were completed and published in peer-reviewed journals in 2010. A literature review on the association between birth outcomes and traffic emissions was published in *Surveys and Perspectives Integrating Environment and Society*. The other study detected an adverse association between the risk of emergency department presentation for asthma and background traffic-related air pollution, and

was published in the *Medical Journal of Australia*. Two other manuscripts are currently under review. The first validated a measure used to assess fetal growth using serial ultrasound scans from the RAINE cohort. The other investigated seasonal variation in fetal growth.

Funders of the project: Australian Postgraduate Award, Perron award, CRC for Asthma and Airways award, Commercialisation Training Scheme award.

## LIVING NEAR AGRICULTURAL PESTICIDE APPLICATIONS AND THE RISK OF ADVERSE REPRODUCTIVE OUTCOMES

Adeleh Shirangi, Mark Nieuwenhuijsen, Danielle Vienneau, C D'Arcy J Holman.

This study was a systematic review of the published literature to evaluate the current epidemiological evidence on the association between living near agricultural pesticide applications and adverse reproductive outcomes. The outcomes considered were: congenital malformations, stillbirth, intrauterine growth retardation (IUGR), low birthweight, preterm birth and miscarriage. We identified and reviewed 25 studies from a systematic search of the main scientific databases and other sources published between 1950 and 2007. Study methods and main results were summarised and tabulated according to the year of study, design and type of adverse reproductive outcome. The levels of evidence for reproductive toxicity in humans contributed by each study were assessed and the main limitations associated with these studies discussed.

Residential proximity to agricultural pesticide applications may be an important source of ambient environmental exposure, but because of the underlying methodological difficulties, the strength of evidence for its relationship with adverse reproductive outcomes is generally weak and varied between outcomes. The evidence suggested an association for congenital malformations, but because of methodological

limitations, such as poor exposure measurement and potentially inadequate control of confounding, a firm conclusion remains beyond reach. For the other outcomes (stillbirth, IUGR, low birthweight, preterm birth and miscarriage) the evidence for any associations was equivocal at best, but some leads warrant further investigation. Improved exposure assessment methods are needed to obtain a more reliable assessment of any risks.

Funding: NHMRC Sidney Sax Overseas Postdoctoral Research Fellowship (AS).

## PARENTAL OCCUPATIONAL EXPOSURE TO POTENTIAL ENDOCRINE DISRUPTING CHEMICALS AND RISK OF HYPOSPADIAS IN INFANTS

Natasha Nassar, Prashan Abeywardana, Andrew Barker, Carol Bower.

There is some evidence that periconceptional parental occupational exposure to endocrine disrupting chemicals (EDCs) with oestrogenic or anti-androgenic properties may adversely affect the development of the male fetal genitalia. In this study, we investigated the association between both maternal and paternal occupational exposure to endocrine disrupting chemicals and hypospadias.

The study used recorded information on 1202 cases of hypospadias born in Western Australia between 1980 and 2000 and a cohort of 2583 male controls randomly selected from birth records for whom information regarding parental occupation was available from the Western Australian Maternal and Child Health Research Database. Occupational exposures to seven groups of potential EDCs were independently coded by two researchers according to a validated job-exposure matrix. We found a strong association with potential maternal occupational exposure to heavy metals with an over two-fold increased risk of hypospadias (Odds Ratio (OR) 2.6, 95%CI 1.3 to 5.2) and women exposed to

phthalates were also more likely to have an affected son (1.2, 0.8 to 1.7). Paternal occupational exposure to polychlorinated organic (OR 1.3, 95%CI 1.0 to 1.8) and bi-phenolic (OR 1.6, 95%CI 1.0 to 2.6) compounds were also possible risk factors. It is important to note that these findings are based on only recorded occupations and do not necessarily relate to actual exposure to EDCs at critical times before or during pregnancy.

Further studies taking into account more detailed parental occupational exposure and possibly, assessment of the effect of genetic susceptibility, are required to elucidate the underlying causes of hypospadias.

NHMRC Postdoctoral Fellowship (NN), NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB)

## Intellectual Disability

### RETT SYNDROME IN AUSTRALIA (AUSSIERETT)

Helen Leonard, Carol Bower, Nick de Klerk, Sue Fyfe, David Ravine, John Christodoulou, Carolyn Ellaway, Lakshmi Nagarajan, Helen Woodhead, Jenny Downs, Carol Philippe, Ami Bebbington, Amanda Jefferson, Olivia Knight, Sonya Girdler.

Rett syndrome is a rare neurological disorder generally affecting females and caused by a mutation in the MECP2 gene. AussieRett, as the Australian Rett Syndrome Study is now 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.

Questionnaires are administered to families on enrolment to the study and then every two to three years. Information is collected at each questionnaire on the affected individual's functional ability in daily living, behaviour, hand function,

medical conditions, and use of health and education services and every four years on family health and functioning. The follow-up questionnaire can be completed by mail, by telephone or over the internet. The study has a Consumer Reference Group which involves regular teleconferences with families across Australia. Genetic and clinical data are also collected as part of the project. The latter include clinical assessments, electroencephalographs (EEGs), electrocardiograms (ECGs), and bone densitometry.

The study has a multi-disciplinary investigative team which includes input from psychologists, physiotherapists and speech pathologists and has national collaborations with the Children's Hospital at Westmead, Sydney and the Royal Children's Hospital, Melbourne. International collaborations also continue with Professor Walter Kaufmann from John Hopkins University and Professor Alan Percy from the University of Alabama.

Progress continues with analytical investigations using data relating to different aspects of the study and during 2010 eleven articles relating to the study were published or accepted for publication. These articles included information about factors affecting the age of diagnosis (such as genotype and aspects of phenotype), the presence of pain insensitivity and the use of equipment and respite services by families) and relationships between their use and maternal well-being. A collaborative study with Austria has investigated survival in Rett syndrome and a number of studies have investigated relationships between genotype and phenotype for example with C terminal mutations and with changes in health status and service use over time. We identified an increased risk of fracture with the use of the anti-epileptic drug valproate and have shown that girls and women with certain MECP2 mutations are more at risk of low bone density. Topics studied by students during 2010 included the trajectory of puberty in Rett syndrome as well as the impact of this disorder on mothers' work practices.

Funders of the project:

US National Institutes of Health (2004-2008), NHMRC Project Grant 303189 (2004-2008), NHMRC Program Grants (353514 and 572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

### RETT SYNDROME: DESCRIBING GROSS MOTOR ABILITIES AND HAND FUNCTION USING VIDEO DATA

Jenny Downs, Ami Bebbington, Peter Jacoby, Kitty Foley, Sonya Girdler, Soumya Ghosh, Walter Kaufmann, Helen Leonard.

Since Rett syndrome is a movement disorder, an extremely important and innovative source of study data is video footage provided by the subjects' families. Many families participating in AussieRett have recorded video footage showing their daughters' participation in activities of daily living, and have provided video footage in 2004 and more recently in 2007/2008. This is an ongoing study.

We have developed validated coding systems for gross motor function and hand function. As cross-sectional studies, data from unique cases have been analysed in relationship to age and genotype, giving a greater understanding of the phenotype of Rett syndrome. Further, we have preliminary evidence to support the validity of the measures that we have developed. These tools that are specific to Rett syndrome could be useful for measuring gross motor and hand function in future clinical trials.

Over 200 families have provided a video of their daughter and some of these on two occasions. We have coded function at two time points approximately 3 ½ years apart to describe the stability of these skills for these subjects. Data analysis for this longitudinal component has been undertaken over the course of 2010. Gross motor skills decreased slightly in approximately 60% of subjects, but teenagers and women who could walk in 2004 were less likely to lose their more

advanced gross motor skills. Hand function skills declined in approximately 40% of subjects, and similarly, this was often observed in girls who were younger and were unable to walk.

The collection of additional videos in Australia is being planned to increase the power of this analysis. We have also piloted the collection of videos showing the same protocol of functional abilities with families with a daughter with Rett syndrome in China. Rett syndrome is a rare disorder, and the video study which includes longitudinal observations is enabling the accumulation of a rich dataset to describe some of the nuances of this disorder.

Funders of the project:

NHMRC Project Grant 303189 (2004-2008), NHMRC Program Grants (353514 and 572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

#### INTERNATIONAL RETT SYNDROME STUDY: INTERRETT

Helen Leonard, Alison Anderson, Nick de Klerk, Sue Fyfe, David Ravine, Ami Bebbington, Sally McIlroy, Stephanie Fehr, Jenny Downs

The InterRett project continues to grow and evolve with ongoing success rewarded with renewed funding for the year ahead. Case ascertainment during 2010 was excellent with submissions from individual families crossing the 1000 mark to reach a total of 1,107 families contributing to a total of 2,240 cases by the year's end. These data were received in a number of languages as families took advantage of the language-specific questionnaires. With a proven record in online data collection, the group is now moving towards an exciting new paradigm in global research: pooled data analysis. During 2010, in collaboration with researchers in Europe and the USA, work began on a framework that will facilitate the pooling of deidentified data from the multiple sites. Under this framework data could be pooled for the investigation of specific research questions without the need for a central

repository. Scientific output and building and maintaining international collaborations is also an ongoing priority. During 2010 three papers that utilised InterRett data were published in the peer-reviewed literature. Further manuscripts in process include two papers arising from our ongoing work with colleagues in China and investigations evolving through recently established relationships with European researchers.

Funders of the project: International Rett Syndrome Foundation.

#### DEVELOPING CLINICAL GUIDELINES FOR THE MANAGEMENT OF SCOLIOSIS IN PATIENTS WITH RETT SYNDROME

Jenny Downs, Ami Bebbington, Philippa Carter, Helen Leonard, Anke Bergmann, Alison Anderson, Greta Palmer, David Roye, Harold van Bosse, Eva-Lena Larsson, Brian Smith, Gordon Baikie, Sue Fyfe, Anne McKenzie, Carolyn Ellaway, Ian Torode, Anne McKenzie, Heidi Meyer.

Scoliosis develops in approximately three quarters of girls with Rett syndrome by 13 years of age. Despite this, there is limited literature of management strategies for scoliosis in Rett syndrome that can support clinical management. Because of the rarity of Rett syndrome, clinicians typically see small numbers of patients and it is difficult to develop significant clinical expertise.

We previously developed clinical guidelines for the management of scoliosis in Rett syndrome based on a systematic review of the literature, the perspectives of parents, and consultation with a multi-disciplinary expert panel of clinicians using a modified Delphi technique. The guidelines follow a life-span approach including comprehensive management techniques relevant to physicians, surgeons and allied health professionals. Specific features of Rett syndrome were taken into account. This project was published in early 2009.

Since publication, we have been implementing a plan for the

dissemination of these results to both clinicians and families. In the first instance, we produced a booklet that described the guidelines in lay language and also summarized the guidelines in the format of a leaflet which was inserted inside the booklet as a handy reference. Hard copies of the booklet have been distributed by mail to families in Australia, in the UK via the Rett Syndrome Association UK, and in the US via the International Rett Syndrome Foundation. They have also been distributed to clinicians participating in the project, to Rett syndrome clinics in the US and to clinicians who have had contact with girls with Rett syndrome in Australia. The booklet and leaflet, including a version translated into Spanish, have been made available on relevant websites.

Funders of the project: International Rett Syndrome Foundation, Rett Syndrome Association of Australia, Rett Syndrome Association UK.

#### 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 Nasseem, Amanda Jefferson, Helen Woodhead, Sue Fyfe, Aris Siafarikas

Rett syndrome is often associated with poor growth, in part from feeding difficulties and/or gastro-oesophageal reflux. Co-morbidities such as constipation and abdominal bloating are also common. Similar to our findings in the scoliosis management study, there is limited literature of management strategies for these common gastro-intestinal disorders in Rett syndrome and we are currently using the Delphi technique to develop a consensus on management. We have recruited an expert panel of clinicians and researchers who have reviewed the first draft of the guidelines. We are currently developing the second draft and will shortly be seeking their consensus on this revision.

Rett syndrome is also associated with osteoporosis and a greater likelihood of fracture in comparison with the general population. We are also developing a set of guidelines for optimal bone health in Rett syndrome. Our methods have thus far included assessment of the perspectives of parents on these issues, systematic review of the literature and the creation of a document for circulation in the first phase of the Delphi process. We are now recruiting an expert panel which is both international and multi-disciplinary in nature who will participate in the Delphi process and provide feedback on the first and subsequent drafts until a consensus is reached.

Funders of the project: Rett Syndrome Association UK.

## DESCRIBING THE CLINICAL PROFILE OF MALES AND FEMALES WITH MUTATIONS IN THE CYCLIN-DEPENDENT KINASE-LIKE 5 (CDKL5) GENE

Helen Leonard, John Christodoulou, Meredith Wilson, Alison Anderson, Ami Bebbington, Stephanie Fehr and Jenny Downs

Rett syndrome is associated with a genetic mutation in the MECP2 gene. However, a small number of those individuals who present with seizures in early life as well as symptoms of Rett syndrome have been found to have a genetic abnormality in the CDKL5 gene rather than MECP2 gene. Mutations in the CDKL5 gene have also been identified in males and females previously diagnosed as West Syndrome or infantile spasms. The characteristics which these conditions have in common are the early onset of seizures generally within the first few months of life, severe psychomotor delay and sub-sequent intellectual disability. Questionnaire and genetic data are being collected through our InterRett Database. Thus far 79 families from 12 different countries (majority being USA and UK) have provided information on their child and these data are being supplemented by further data from the child's clinician. Photographs of the face, hands and feet are also being collected and will be used along with the clinician and family data to investigate the hypothesis that these individuals

share a characteristic facial gestalt. This work is being carried out in collaboration with Professor John Christodoulou and clinical geneticist and dysmorphologist Dr Meredith Wilson both from the Children's Hospital at Westmead in Sydney.

Funders of the project: International Rett Syndrome Foundation.

## AUSTRALIAN-CHINA ALLIANCE: INVESTIGATING THE RELATIONSHIP BETWEEN GENOTYPE AND PHENOTYPE IN RETT SYNDROME

Helen Leonard, Alison Anderson, Sue Fyfe, John Christodoulou, David Ravine, Jenny Downs, Stephanie Fehr and Faye Lim.

Three members of the Australian research team visited Beijing in early 2010 to continue collaborative efforts with the Beijing research team. As part of this ongoing collaboration with China, a study investigating the pathways leading to a diagnosis of Rett syndrome in China was recently completed. It was found that limited clinician knowledge and information on rare disorders, such as Rett syndrome, was a key factor preventing families from receiving a diagnosis. The experiences of Chinese families caring for a child with a severe disability were also examined. Parents commented that there was a lack of information and support available to them. We are currently in the process of discussing the development of a support association for Chinese families affected by Rett syndrome.

The feasibility of collecting video data from Chinese families for future clinical studies was also investigated. We found that some parents had difficulties returning their completed videos to us and the use of online uploading systems is a priority for future research.

In conjunction with our Chinese colleagues we have also recently investigated the parental origin of MECP2 mutations. We found that although the majority of mutations are found on

the paternal derived X-chromosome, those of maternal origin are more likely to be associated with a different mutation type (e.g single nucleotide insertions or deletions). These findings raise questions about the mutational mechanism behind the MECP2 mutations and also the impact this has on recurrence risk and therefore genetic counselling regarding future pregnancies.

Funders of the project: DEST Australia-China Fund (Department of Education, Science and Training) and International Rett Syndrome Foundation.

## IDEA - INTELLECTUAL DISABILITY EXPLORING ANSWERS

Helen Leonard, Jenny Bourke, Carol Bower.

The IDEA Database provides an infrastructure for population-based epidemiological and genetic research into the causes and prevention of intellectual disability. Information in the database is based on data from the Disability Services Commission (DSC) since 1953, as well as information from the Department of Education for births since 1983. IDEA is currently updated with notifications of children identified with an intellectual disability from the Department of Education and the Disability Services Commission to the end of 2008. 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. Further improvement of records currently in the database has occurred through the provision of medical information from DSC.

Analysis of 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. This rise will be investigated to see if the increase is represented by an increasing number

of diagnoses for autism spectrum disorders or another identifiable cause.

Whilst no new studies applied for approval to link to the database in 2010, updated data were provided for a study of health outcomes and use of hospital services by women with a recorded alcohol-related condition during pregnancy and their offspring. Tabular data were provided for a PhD study on accommodation support for Western Australians with intellectual disability. Articles published in the scientific literature during 2010 using data from the IDEA database have covered the areas of autism prevalence, child maltreatment, evaluation of family-centred care for children with intellectual disability, hospital admissions of children and adolescents with single gene and chromosomal disorders and variation over time in health conditions of children with Down syndrome.

The IDEA Advisory Council met on November 23, 2010. 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 Chauvel (Paediatrician), 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, Marie-Louise Collins, Carol Philippe, Sarah Tocker, Kitty Foley, Sonya Girdler.

This 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. 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. 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 will spend their days.

This study involves young people with intellectual disability aged 16 years and over from four separate cohorts: i) WA (Down syndrome NOW), (ii) the Queensland Centre for Intellectual and Developmental Disability's ASK cohort which is 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) Rett syndrome Australia-wide. We used the World Health Organization's International Classification of Functioning, Disability and Health (ICF) framework which enables us to take into account the complexity of life and acknowledges that many things come into play which may affect a person's participation in all aspects of life. Environmental factors, which in this study will include family characteristics such as income, availability of transport, parental health and family functioning, as well as the health of the child and their individual level of functioning, may all contribute to the young person's participation in society.

Two hundred and sixty eight families in WA with a young person with Down syndrome received a questionnaire. Their ages varied from pre-transition (16-17 years), early transition (18-20 years) to late transition (23-31 years). Three quarters of these families live in the metropolitan area. Most young people lived at home with their parents

or guardian. One hundred and thirty six questionnaires were also sent out in November 2009 to families and care workers of girls and young women with Rett syndrome aged 16 years and over throughout Australia. Of these, 126 (92.6%) have been returned. In consultation with the WA research team and based on our model of collection and storage of data the Queensland group developed a questionnaire and administered it to their cohort. 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.

Preliminary findings suggest that the employment needs of about one third of the young people with Down syndrome in Western Australia were not being met in 2009/2010. This would suggest that services and interventions may not be adequate or appropriate for enabling young adults with Down syndrome to enter the work force. Further analysis will try to identify the factors which are affecting later outcomes and explain why some young people are finding suitable employment while others are not.

Funders of the project: Australian Research Council, NHMRC Fellowship #634341 (CB).

#### **WA REGISTER FOR AUTISM SPECTRUM DISORDERS**

Emma Glasson, Sarah MacDermott, 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 2010 information has been collected on approximately 4,000 individuals.

As well as existing for the purpose of local and national information, Register data were used in an international collaboration making comparisons with a Danish autism register. This project was awarded funding from Autism Speaks (USA) and findings are due to be published in the Journal of Autism and Developmental Disorders during 2011.

Funding and support for the WA Register for Autism Spectrum Disorders during 2010 included the Disability Services Commission of WA and Autism Speaks (USA).

### WESTERN AUSTRALIAN AUTISM BIOLOGICAL REGISTRY

Andrew Whitehouse, John Wray, David Ravine, and Anna Hunt.

Autism Spectrum Disorder (ASD) is a serious lifelong developmental disorder characterised by impairment in reciprocal communication and social interactions, as well as cognitive and behavioural inflexibility. While the biological pathways contributing to ASD remain poorly understood, current consensus is for a multifactorial aetiology, incorporating a constellation of genetic risk variants, perhaps interacting with environmental factors.

The aim of the Western Australian Autism Biological Registry is to collect detailed information on newly diagnosed cases of ASD in WA. By collecting in-depth information on a large number of children, our hope is to identify biological factors of small effect that may be overlooked in smaller samples.

Children are assessed at the Institute, where they are administered a range of behavioural tests. Blood samples are also obtained from children and their parents, which are then analysed for genetic material. To date, 100 children have undergone this procedure, and we anticipate that a further 100 children will be seen during 2011.

Funders of the project: Department of Health, University of Western Australia.

### FLUOXETINE FOR THE TREATMENT OF RESTRICTED, REPETITIVE AND STEREOTYPED BEHAVIOURS IN CHILDREN AND ADOLESCENTS WITH AN AUTISM SPECTRUM DISORDER: A RANDOMIZED CONTROLLED TRIAL

Andrew Whitehouse, John Wray and Jo Granich.

Restricted, repetitive and stereotyped behaviours are a key feature of Autism Spectrum Disorder (ASD), and are often disruptive to the quality of life of affected individuals and their families. Selective serotonin reuptake inhibitors (SSRIs), such as Fluoxetine (tradename: Prozac), are commonly prescribed to target the anxiety that is thought to exacerbate these behaviours in people with ASD. However, there is little empirical evidence demonstrating the safety and effectiveness of Fluoxetine with this population.

The aim of this project is to investigate the safety and efficacy of low dose liquid Fluoxetine in the treatment of restricted, repetitive and stereotyped behaviours in children and adolescents with an ASD diagnosis.

Individuals with ASD aged 8-18 years (n = 146) will take part in a multi-site (Western Australia, Victoria and New South Wales) randomized double-blind placebo controlled trial of Fluoxetine. The trial is conducted over a 22 week period, during which time participants will be administered either Fluoxetine or placebo syrup daily. Individual ASD symptoms will be assessed pre- and post-trial using the CY-BOCS-PDD compulsion scale; Repetitive Behaviour Scale (RBS-R); Spence Children's Anxiety Scale (SCAC); Aberrant Behaviour Checklist (ABC); and the Clinical Global Impressions Scale (CGI). Tolerance and side-effects checklists will also be utilised.

This is the largest trial of the effectiveness of Fluoxetine for children and adolescents with ASD ever conducted. It is hoped that this trial will provide valuable information on whether medication could be a helpful complement to traditional behavioural intervention for children with ASD.

Funders of the project: National Health and Medical Research Council.

### MULTI-REGISTRY ANALYSES OF PRE- AND PERINATAL RISK FACTORS FOR AUTISM

Michaeline Bresnahan, Kim Carter, Richard Francis, Mika Gissler, Raz Gross, 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 and Ezra Susser.

Population-based disease registry systems are extremely important research resources especially for conditions such as autism which are of comparatively low prevalence. Yet despite numerous studies investigating the association between pre- and perinatal factors and autism, many relationships remains 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, 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 are being used to create a common set of variables across all sites. Using the bioinformatics expertise at the Institute the data will then be pooled to create a virtual dataset allowing the use of data from all countries/states to investigate the relationships between pre and perinatal factors and autism. This virtual dataset will also allow cross-country comparisons, and ensure that common methodologies are used.

Funders of the project: Autism Speaks.

## WA Cerebral Palsy Studies

Eve Blair, Linda Watson, Jan de Groot, Fiona Stanley.

Cerebral palsy (CP) is a chronic neurological condition affecting movement and posture, ranging in severity from barely noticeable to severely disabling. For most, the cause is unknown. CP results in life-long disability, and as there is no cure, prevention and effective management are top priorities.

### THE WESTERN AUSTRALIAN CEREBRAL PALSY REGISTER

Linda Watson, Eve Blair, Fiona Stanley.

The WA CP Register, now in existence more than 30 years, 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 2004.

The WA Register is now also responsible for contributing data to the Australian CP Register (ACPR), a national collaboration initiated by the WA team which was established to provide information about CP throughout Australia as well as a larger study population to enable more effective research. The administrative centre has now moved to the Cerebral Palsy Institute in NSW where it continues to flourish. The first report of the ACPR was published at the very end of 2009, Eve Blair presented the results of this report both at the AusACPDM meeting in Christchurch New Zealand and at the AACPD meeting in Washington, USA.

### DEVELOPING A RELIABLE SYSTEM OF CLASSIFYING 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 research therefore depends on consistency in classifying CP subgroups. International attention has been focused on the challenge of standardising the recording of motor impairments for several decades, and WA has long been at the forefront in developing a reliable system of describing the clinical features of CP. We are continuing to introduce and trial an innovative diagrammatic limb-by-limb CP Description Form which incorporates the Australian Spasticity Assessment Scale (ASAS) devised by Sarah Love and Noula Gibson, who have led this work. A booklet which defines every aspect of the form is currently being compiled. A Training and Reference video demonstrating the use of the ASAS as well as the features of different forms of CP is also in preparation.

Funders of the project:

The WA Cerebral Palsy Register and Case-control Studies were funded by NHMRC Program Grant #353514 (2005-2009). PLAN Australia has generously funded the development of the ASAS, the CP Description Form and the Training and Reference DVD. A PMH Foundation Special Project Grant 2007 covers travel to conduct training sessions throughout WA, and an Innovative Research Grant from the CP Institute funds the extension of training across Australia.

### CASE CONTROL STUDIES OF CP IN TERM AND PRE-TERM INFANTS IN WA, 1980 TO 1995

Jan de Groot, Eve Blair, Kate Taylor, Sarah McIntyre, Linda Watson, Fiona Stanley.

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 providing a wealth of data enabling causal pathways to the different outcomes to be compared. 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 international forums.

Funders of the project:

The WA Cerebral Palsy Register and Case-control Studies were funded by NHMRC Program Grant #353514 (2005-2009). PLAN Australia has generously funded the development of the ASAS, the CP Description Form and the Training and Reference DVD. A PMH Foundation Special Project Grant 2007 covers travel to conduct training sessions throughout WA, and an Innovative Research Grant from the CP Institute funds the extension of training across Australia.

## 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 into 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 2010:

Maternal folate and other vitamin supplementation during

pregnancy and risk of acute lymphoblastic leukemia (ALL) in the offspring

We found that taking folic acid or other vitamins during pregnancy did not change the child's risk of ALL. There was some evidence that taking folic acid before pregnancy may slightly reduce the risk of the child getting ALL, but this needs to be looked at in larger studies. When we combined our results with those of other studies from around the world, there was evidence that taking multi-vitamins during pregnancy may reduce children's risk of getting ALL. We could not determine whether a specific vitamin was responsible for this association.

Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study

We found that drinking coffee or tea during pregnancy generally did not change the child's risk of ALL. There was some evidence that among mothers who did not smoke, the risk was slightly increased if the mother drank more than 2 cups of coffee a day, which is similar to what we found when we combine our results with those from other studies around the world. There was some evidence that the risks of drinking tea or coffee may be different for particular types of ALL, but we did to look at this further in larger studies.

Exposure to diagnostic radiological procedures and the risk of childhood acute lymphoblastic leukemia

We found that the mother having an abdominal x-ray before or during her pregnancy or the child having any x-rays did not change the child's risk of ALL. There was some evidence that the father having more than abdominal x-ray or special types of x-rays before the child's conception could increase the risk of the child getting ALL, but this needs to be looked at in larger studies.

Representativeness of child controls recruited by random digit dialing

In this paper, we described how the controls in this study were recruitment by telephone using random digit dialing. We found that control families who agreed to take part in the study and completed the study questionnaires lived in areas of higher socio-economic status than the general population. This finding needs to be considered when we are analyzing the other information collected in the study.

Analysis is also under way to examine whether there are links between risk of ALL and:

- the mothers' diet during pregnancy;
- exposure to house painting
- exposure to pest control treatments in the home or garden
- the types of jobs that parents had
- Parental smoking and alcohol consumption
- variations in genes that influence the way the body processes food and chemicals

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 Allesandri.

The Australian Study of Childhood Brain Tumours (AUS-CBT) is a national case-control study into the causes of childhood brain tumours (CBT). It aims 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 has been recruiting case and control families since 2006; recruitment and data collection will be finishing in June 2011.

The study involves children aged 0-14 years. Case children and their parents are recruited from the nine paediatric oncology units nationwide. At the end of 2010, we had been notified of 654 eligible cases, of whom 554 (84.7%) were invited to participate and 354 (54.1%) consented. A total of 103 families have declined to participate and a further 68 were not invited due to medical and psychosocial reasons. Recruitment is ongoing and we are liaising with clinicians regarding further invitation and consent of the eligible families.

Control families were recruited through national random digit dialing and are frequency matched to the case children by age, gender and State of residence. The control children have not been diagnosed with a CBT. AUS-CBT control family recruitment began in 2007 and nine waves have been completed, with 807 families agreeing to participate when contacted by phone. Of these, 511 (63.3%) have given their consent. Control recruitment has now finished and we are continuing to finalise data collection from these families.

The data collected include self-administered exposure questionnaires for both parents, food frequency questionnaires for both parents and the child, and telephone interviews regarding occupational and other exposures. In addition, we are collecting DNA samples from either blood or saliva for genotype analysis. Data collection for both the case and control families is progressing well. At the end of 2010, we had received exposure questionnaires from 774 families, food frequency questionnaires from 637 families and we had conducted 1221 telephone interviews. DNA samples had been provided by 525 families (including samples from the child and both parents), and 2092 samples had been sent for genotyping.

As the study comes to an end, we are continuing to aim for

the highest possible participation and response fractions in completing the data and DNA collection stages of the study.

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 aims to identify key nutritional and genetic factors that may be associated with DNA damage in children. It looks 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 is a cross-sectional study of 450 Western Australian children, conducted between 2009 and 2011. Participants are children aged 3, 6 or 9 years at recruitment who have never been diagnosed with asthma, diabetes, cancer, arthritis or epilepsy. Participants and their parents are recruited via primary schools, posters displays and flyers, advertisements in local newspapers and information letters distributed to a wide range of organizations. These include crèches, day care centres, playgroups, sports centres and libraries.

The study assesses the child's diet and macro- and micro-nutrient intake by using parent-completed Food Frequency Questionnaires (FFQs). A sample of the child's blood is taken and used to assess micronutrient levels and specific biomarkers of DNA damage. The blood sample is also used to identify genetic polymorphisms related to nutrient metabolism and DNA repair. Saliva samples collected from the child are used to measure cortisol and cotinine levels, as indicators of psychological stress and exposure to environmental tobacco smoke, respectively. When the questionnaires and samples have been processed, parents are provided with feedback on their child's diet, and dietary advice is provided by a dietitian if

needed.

The study started in February 2009 and will continue until December 2011. The study is progressing well and is on track to complete participant recruitment by mid-2011. By the end of 2010 we had 381 active parent consents (101 three-year olds, 126 six-year olds and 154 nine-year olds). Of these, 347 participants had completed all data collection. All participants in progress or with queries will be followed up to obtain a complete and accurate data set.

From the data collected, 354 saliva samples have been analysed for cotinine and cortisol, and 366 Food Frequency Questionnaires (FFQ) have been entered in FoodWorks nutrient analysis package. Feedback letters, detailing the children's blood vitamin B12 and folate levels and their reported dietary intake as well as the recommended values, have been sent to the first 300 participants. Statistical data analysis is in progress.

Funders of the project: NHMRC Grant#572623.

## Infectious Diseases

### AETIOLOGY, BURDEN AND CAUSAL PATHWAYS OF ACUTE LOWER RESPIRATORY INFECTIONS USING POPULATION LINKED DATA

Hannah Moore, Deborah Lehmann, Peter Jacoby, Nicholas de Klerk in collaboration with Peter Richmond, David Smith, Tony Keil.

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. Data analysis and dissemination of results was the focus for 2010. Major findings

were:

- Pneumonia hospitalisations declined in all children, particularly in Aboriginal children. Between 1996-2000 and 2001-2005 all-cause pneumonia hospitalisation rates fell by 28-44% in Aboriginal children aged 6-35 months. Hospitalisations for pneumococcal pneumonia have declined by 37%/annum in Aboriginal children aged 6-11 months.
- Disparity in pneumonia hospitalisations between Aboriginal and non-Aboriginal children aged 6-11 months has declined from being 15 times higher in Aboriginal children compared to non-Aboriginal children in 1996-2000 to 10 times higher in 2001-2005.
- Factors leading to increased risk of ALRI for both Aboriginal and non-Aboriginal children are: being born in autumn, high parity, male gender and maternal smoking during pregnancy. In Aboriginal children, being born to a teenage mother and poor socio-economic status have been identified as major risk factors.
- Non-Aboriginal children delivered by elective caesarean have an increased risk of repeated hospitalisations for bronchiolitis compared to those non-Aboriginal children who were delivered through spontaneous vaginal delivery.

Some of these findings have been published in international peer-reviewed journals and were presented at the 7th International Symposium on Pneumococci and Pneumococcal Diseases, the Australasian Epidemiological Association Annual Meeting and various other local meetings.

Data were received from PathWest Laboratory Medicine in 2010. These data represented routine respiratory pathogen testing between 2000 and 2005 for children in the birth cohort. Cleaning these data was also a major focus for the year. The cleaned dataset consists of positive and negative identifications of 30 viral and bacterial respiratory pathogens predominately from nasopharyngeal aspirates. These

laboratory data were then merged with hospital episodes for ALRI and asthma between 2000 and 2005. Approximately 38% of hospital records for ALRI and asthma linked to a laboratory record where the date of specimen collection was within 48 hours of a hospital admission. Analysis of these data to describe the aetiology of ALRI will be the focus of 2011. Data were also received from the Birth Defects Registry. These data will be analysed in 2011 to investigate whether children born with a birth defect have a higher risk of ALRI than children without a birth defect.

Funders of the project: NHMRC Project Grant #572590.

## PREVENTING OTITIS MEDIA TO GIVE A SOUND START FOR SCHOOL

Deborah Lehmann, Ruth Monck, Wendy Sun, Margaret Wallam, Daniel McAullay, Tanyana Jackiewicz in collaboration with Anne Mahony, Charles Douglas, Michelle Forrest, Bega Garnbirringu Health services, Ngunytyu Tjitji Pirni Inc, Francis Lannigan, Sharon Weeks, Annette Stokes, Christine Jeffries-Stokes.

This 3-year project follows on from findings of the Kalgoorlie Otitis Media Research Project. 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 Community Health Nurses and Aboriginal Health Workers 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.

Following training of health professionals in August 2009 and development of a flowchart for diagnosis and management of otitis media, ear screening began in Kalgoorlie, Laverton, Leonora, Menzies and Coolgardie. The project team made 7 visits to the remote communities in the Goldfields. 113 children under the age of 5 years from Kalgoorlie and surrounding communities were enrolled. Out of 103 valid ear examinations, 42% needed further management (e.g. topical or systemic antibiotics or referral to an audiologist or ear specialist). Thus 43% of children with valid results had OM. There has been a large increase in referrals to Dr Lannigan's clinic at Bega Garnbirringu Health Services. A highlight was Dr Lannigan's clinic in Leonora, the first ear specialist to visit the town in living memory.

In order to evaluate the impact of the awareness and health promotion program we have interviewed some community members to assess knowledge and practice around ear disease, smoking, hand washing practices prior to the program in clinics and in the public. This will be repeated at the end of the project in 2012.

In addition to holding ear health promotion events and being part of local public events such as NAIDOC week and Children's Day, 8 soap-making workshops with community members and 23 music workshops with 4 groups of school students have been conducted in 2010. These workshops were

well received in communities. People found the educational tools, namely the video-otoscope and the "GlitterBug", fascinating. Through fun activities, local community members were reminded that frequent hand washing can help prevent ear and other infections. People also commented they "would like more activities to get people out of the house and away from drinking". During music workshops school age children learned about the ear through singing songs. The musical tells of the impact OM can have on schooling and self-esteem and ways of preventing it. The play gave students self-confidence to perform in front of audiences.

The workshops also attracted considerable media attention with photos and articles in the Kalgoorlie Miner newspaper and local community newsletters which further promoted the project and spread the health promotion messages to the wider community.

The study was presented at:

- OMOZ 2010 Australian Otitis Media Workshop on 26 May 2010 in Darwin
- Start Stronger, Live Longer Aboriginal Health Worker Conference on 8 June 2010 in Perth

Funders of the project: Western Australian Health Promotion Foundation (Healthway).

## HOSPITALISATION FOR DIARRHOEA AMONG WESTERN AUSTRALIAN CHILDREN

Deborah Lehmann, Karthik Raj Manoharan, Hannah Moore.

Diarrhoea is a significant reason for hospitalisation in Australia. This study utilising the total population-based databases from the Maternal and Child Health Research Database investigates the trends in hospital admissions for diarrhoeal diseases (gastroenteritis) in Western Australian children aged <math>\leq 15</math> years between 1983 and 2006. Hospitalisation rates for gastroenteritis are highest

in children aged 6-12 months. In Aboriginal children aged 6-11 months, rates have fallen from 290 per 1000 population in 1987 to 153/1000 in 2006 with similar declines in other age groups. In non-Aboriginal children, hospitalisation rates for gastroenteritis have remained constant around 20/1000. This study will be useful in providing baseline data on hospitalisations for diarrhoeal disease prior to the introduction of the rotavirus vaccine in 2007. These findings will now be collated for a publication.

Funders of the project: NHMRC Program Grant #353514.

#### MONITORING CARRIAGE OF STREPTOCOCCUS PNEUMONIAE AMONG ABORIGINAL CHILDREN AND ADULTS IN WESTERN AUSTRALIA

Deborah Lehmann, Anke Bergmann, in collaboration with Jacinta Bowman, Jade Jones, Tom Riley, Carolien Giele, Paul Effler, Amanda Leach, Kim Hare, Heidi Smith-Vaughan, Peter Richmond.

*Streptococcus pneumoniae* (pneumococcus) can cause middle ear infections and invasive pneumococcal disease (IPD) such as meningitis, pneumonia and septicaemia (blood poisoning). The Australian Aboriginal population has among the highest reported IPD rates worldwide. The existence of 92 known types (serotypes) of pneumococci increases the challenge of prevention. A pneumococcal conjugate vaccine (Prevenar™) covering the 7 most common serotypes causing IPD and a booster with a pneumococcal polysaccharide vaccine (Pneumovax™) covering 23 serotypes has been offered to Aboriginal children since 2001. Pneumovax is also offered to adults. While there has been a marked reduction in overall IPD rates as a result of almost complete elimination of disease due to Prevenar serotypes, there has been some increase in IPD rates due to serotypes not included in Prevenar, particularly a marked increase in young Aboriginal adults. The findings of replacement disease due to non-vaccine serotypes in the Western Australian Aboriginal population is consistent with

data from elsewhere. Hence a need for new vaccines covering a broader range of serotypes causing IPD has been recognised and our data will help inform policy regarding formulation of future vaccines. Two candidate vaccines (one covering 10 pneumococcal serotypes, the other 13 serotypes) have been licensed in Australia recently.

Pneumococci are carried in the back of the nose of healthy as well as sick individuals. 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, thereby informing public health programs. It also gives a conservative estimate of antibiotic resistance of invasive pneumococcal strains. This study aims to monitor pneumococcal carriage by collecting 600 pernasal swabs annually 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 information on immunizations given to children as well as adults.

Other study aims include:

- i) describing the prevalence of upper respiratory tract (URT) carriage of other pathogens identified on primary culture;
- ii) comparing pneumococcal carriage rates in Aboriginal children aged < 2 years in the Kalgoorlie-Boulder region with those documented in 1999-2005;
- iii) comparing the distribution of pneumococcal serotypes in the URT with those causing IPD in Aboriginal adults and children annually;
- iv) storing pernasal swabs for detection of viruses by PCR to describe the prevalence of respiratory viruses; and
- v) investigating viral-bacterial interactions in the URT.

We recruit study participants attending health services for routine examination, immunisation or illness and also through home-visiting or community links. To date we have

collected 1054 pernasal swabs and 34 swabs of discharge from the middle ear from a total of 359 children aged < 5 years and 695 older children and adults. Recruitment has taken place in Wiluna, Kalgoorlie, Coolgardie, Roebourne, Wickham, Kununurra, Broome, Beagle Bay, Carnarvon, Jigalong, Meekatharra, Burringurrah, Bunbury, Geraldton and at Aboriginal Medical Services in the Perth Metropolitan area (Perth, Armadale, Bentley, Maddington, and Kwinana). 987 pernasal swabs have been cultured to date.

In children under 5 years of age pneumococci have been grown from 68% of pernasal swabs, *Haemophilus influenzae* grew in 60% of swabs and *Moraxella catarrhalis* in 63%. In people aged > 5 years 33% of pernasal swabs grew pneumococci, 19% grew *Haemophilus influenzae* and 25% grew *Moraxella catarrhalis*. 39 different serotypes have been identified and an unknown serotype belonging to serogroup 6 has been isolated and is currently being investigated further. Currently the most common serotype in children are 19A, 11A and 16F, while serotypes 34, 16F and 11A are most common in those aged > 5 years.

In line with data from IPD surveillance in WA, Prevenar has successfully eliminated carriage of serotypes included in this vaccine since only 10% of pneumococci are Prevenar serotypes. In contrast, 56% of pneumococci in the URT are serotypes that are not covered by either Prevenar or one of the two recently licensed pneumococcal vaccines which clearly indicates that ongoing surveillance of pneumococci carriage is crucial for development of new vaccines and immunization guidelines for Aboriginal people.

Our findings to date have been presented at the 7th International Symposium on Pneumococci and Pneumococcal Diseases in Tel Aviv in March 2010 and the Australian Otitis Media Workshop in Darwin in May 2010.

Funders of the project:

Western Australian Department of Health through the

Collaboration for Applied Research and Evaluation and NHMRC Project Grant #545232 (a collaboration with Menzies School of Health Research).

### 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, Christine Jeffries-Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane, Ruth Monck, Fiona Stanley, in collaboration with Bega Garberringu Health Services, Ngnyntju Tjitji Pirni Inc, Harvey Coates, Thomas Riley, Sharon Weeks, Allan Cripps, Jennelle Kyd, Jacinta Bowman, Amanda Taylor, Gerry Harnett, David Smith, 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.

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, and 65% of Aboriginal children and 23% of non-Aboriginal children have some degree of hearing loss at age 12-17 months.

We found that 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 that 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*. The findings have been accepted for publication in an international journal.

Rhinoviruses and adenoviruses are commonly identified in the upper respiratory tract, more commonly in Aboriginal than non-Aboriginal children and are frequently associated with bacterial carriage. We reported in an international journal that rhinoviruses were associated with carriage of *Haemophilus influenzae* and *Moraxella catarrhalis* in Aboriginal children. Adenoviruses were positively associated with carriage of *H. influenzae* in Aboriginal children and *M. catarrhalis* in non-Aboriginal children, but negatively associated with *Streptococcus pneumoniae* in Aboriginal children.

We also found that early onset of bacterial carriage increases the risk of subsequent OM. Early carriage of *H. influenzae* increases risk of OM in Aboriginal children, while early carriage of *M. catarrhalis* increases risk of OM in non-Aboriginal children. The likelihood of developing OM is higher following simultaneous carriage of *S. pneumoniae* and *H. influenzae* than if either pathogen is carried alone. A manuscript is in preparation.

We investigated antimicrobial susceptibility of *M. catarrhalis* strains isolated from children in this study. A large proportion of 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. These findings have been published in an international journal. We have also documented for the first time simultaneous carriage of multiple strains of *M. catarrhalis*. N Pingault's PhD thesis on the epidemiology of *M. catarrhalis* has been submitted and

passed.

Finally analyses investigating associations between mucosal immunity and upper respiratory tract carriage are progressing well in collaboration with A Cripps and S Occipinti.

Funders of the project:

Western Australian Health Promotion Foundation (Healthway); NHMRC Project Grant #212044 and as part of the NHMRC Program Grant #353514.

### INFECTIOUS DISEASES COMMUNITY REFERENCE GROUP

Deborah Lehmann, Hannah Moore, Kirsten Alpers, Anne McKenzie.

In 2007 we convened an Infectious Diseases Community Reference Group to inform the wider community about research conducted at ICHR around infectious diseases and for community members to provide researchers with their valuable input into research projects. This group consists of 13 members including 8 community members (of which 4 are Aboriginal), 2 researchers, 1 representative from the Western Australian Department of Health, 1 representative from the Vaccine Trials Group and 1 representative from the Institute for Child Health Research Consumer and Community Advisory Council. The current members of this group are: Barry Combs, Bev Taylor, Glenn Pearson, Helen Martin, Jane Jones, Karen Ziegelaar, Linda Gibbs, Maude Walsh, Megan Scully, Natasha Indich, Patricia Nyaga, Rae Young and Trish Laitt. This group met four times in 2010 and discussed the progress of the research projects associated with infectious diseases at ICHR. In September 2010, members of this group participated in a community conversation. This consisted of focus group sessions around four key areas: what infectious disease research should we be conducting, how we can increase community participation, how can we feedback the results of our research to the community and what are the major concerns around vaccines.

Funders of the project: Jointly funded by the Meningitis Centre and NHMRC Project Grant #572590.

### NEONATAL IMMUNISATION WITH PNEUMOCOCCAL CONJUGATE VACCINE IN PAPUA NEW GUINEA

Deborah Lehmann, Anita van den Biggelaar, Pat Holt, in collaboration with Peter Siba, William Saila Pomat, Suparat Phuanukoonnon, John Reeder, Peter Richmond, Amanda Leach, David Smith.

Throughout the world an estimated 820,000 children die annually from pneumococcal disease, the majority in early infancy. 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 will provide earlier protective antibody responses. The study is assessing the impact of a 7-valent PCV (7vPCV) on early pneumococcal nasopharyngeal colonisation and on the incidence of acute respiratory infections in the first year of life. We are investigating the development of mucosal and T-cell immunity to non-capsular pneumococcal protein antigens and how this may be affected by early onset of colonisation. The study is also assessing 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.

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, and in a neonatal or early infant schedule primes for immunologic memory for 7vPCV serotypes with booster response to 23-valent pneumococcal polysaccharide vaccine (23vPPV) at age 9 months and sustained serotype-specific antibody

concentrations to age 18 months. PPV also induces good antibody responses for some pneumococcal serotypes that are not included in PCVs but which commonly cause disease. 70% of neonates 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 were non-7vPCV serotypes. 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 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.

A multiplex PCR at PathWest Laboratory Medicine WA has been used to identify viruses in the nasopharynx of sick and healthy trial participants. Influenza viruses, respiratory syncytial virus and adenoviruses were more common during episodes of acute lower respiratory tract infections while coronaviruses and rhinoviruses were as prevalent as when children were healthy.

Assays to measure mucosal immunity to pneumococcal polysaccharides are currently being optimized in the laboratories in Goroka.

Funders of the project: This study was funded by the NHMRC/ Wellcome Trust International Collaborative Research Grant #303123.

### 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 in collaboration with Peter Siba, William Saila Pomat, Andrew Greenhill, Christine Opa, Gerard Saleu

Recently, concerns have been raised about the role of the pneumococcal polysaccharide vaccine (23vPPV) 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) 23vPPV 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) there is a sustained serotype-specific pneumococcal antibody responses up to age 18 months with a 23vPPV booster at age 9 months following priming with 3 doses of 7vPCV. Nevertheless it is important to ensure the immunological safety of the 23vPPV in infants.

This study aims to determine whether 23vPPV given at 9 months of age:

1. provides enhanced persistence of antibody levels associated with protection from invasive disease at 3 to 4 years of age compared to unvaccinated controls
2. has an impact on the development of serotype-specific B-cell memory at 3 to 4 years of age
3. enhances antibody persistence and B-cell memory for those serotypes included in 7vPCV among children who received 7vPCV in early infancy.

We are assessing immune function (by measurement of serotype-specific antibody titres, opsonophagocytic antibodies

and memory B-cell responses) and nasopharyngeal carriage before and one month after a small dose (0.1ml) of 23vPPV in children who took part in the previous neonatal 7vPCV trial (described above) and in 150 age-matched controls at age 3-4 years. We are also collecting data on incidence of acute lower respiratory tract infections in all study participants by medical record review. In 2010 110 children who had previously received PCV and PPV have been enrolled and 90 con-trols.

Funders of the project: PNGIMR/AusAid

## Collaboration for Applied Research and Evaluation

### CASE STUDY PROJECT

Roz Walker.

This project involved a comprehensive review of relevant national and international studies, policies and best practice which informed the study objectives and identified future research areas. The literature includes studies of pathways to ADHD diagnosis, the barriers and facilitators and their implications for this study. Stage 2 involves in depth interviews with parents of children with ADHD that meet the selection criteria. Interviews focused on their experiences along the pathway to a diagnosis of ADHD for their child/children, including their beliefs, knowledge and attitudes regarding ADHD; and the external barriers and facilitators that inform and influence their choices. The initial process to recruit families into the study was unsuccessful. A revised process was agreed upon by the DoH and ethics was resubmitted and approved. Clinicians, (paediatricians and child psychiatrists) across the metropolitan area in both public and private practices identified eligible families who agreed to participate in the study. A case study methodology was used. The case studies showed that all parents in the study have tried alternative treatments to medication, many parents are

profoundly impacted by the ongoing severity of their child's/ children's condition; several families have multiple children with ADHD, many of these children have other co-morbidities but the primary treatment is for ADHD, or the best outcomes for their child occurred after diagnosis and treatment for ADHD, many families feel complete isolation, alienation and stigma. Most expressed concerns about their child expressing suicidal thoughts or attempting suicide. Several families had experienced separation or divorce which they attributed to their partner not coping with their child/children's condition, had chosen to send their child/children to private school and secure private tuition to have additional academic and pastoral support, many were experiencing significant financial burden due to school and medical expenses for alternative treatments, special diets, and replacement of damaged households items.

Interviews were completed in July 2010; and the final report with recommendations will be completed in February 2011:

- A review of the relevant literature in the area of ADHD pathways to diagnosis.
- A series of case studies outlining the families experience along the pathway to diagnosis.
- A set of themes that will be used to inform future phases of this research.
- A review and refinement of the Pathway to Diagnosis Model proposed by Smith (2007), and
- Recommendations.

Funders of the project: Western Australian Department of Health.

### INFANT FEEDING IN WESTERN AUSTRALIA: ESTABLISHING A BASELINE AND EVALUATING THE WA DEPARTMENT OF HEALTH'S BABY FRIENDLY HEALTH INITIATIVE POLICY (BFHI)

Grant Smith, Tanyana Jackiewicz, Alicia Watkins

To undertake a state-wide population-representative survey with the aims of 1) determining the relationship between hospital practices (and community services) and breastfeeding practices 2) identifying whether the DOH BFHI policy rollout was associated with improved infant feeding practices in WA, and 3) obtaining a reliable baseline measure on prevalence of breastfeeding in WA.

The initial (baseline) survey of 1054 mothers with children aged 9 months across Western Australia was conducted in 2010 using computer assisted telephone interviewing with the assistance of the ECU Survey Research Centre. Mothers were asked about their experiences in hospital that relate to BFHI practices; they were asked about their infant feeding practices including duration, introduction of formula and other liquids and the introduction of solids. Finally they were also asked about their experiences with community services aimed to improve infant feeding practices.

Preliminary data analyses have been conducted and the results presented at the Women's and Newborns' Health Network Research Symposium in November. The main conclusion of the first phase data collection is that a mother's experience of breast feeding conducive practices whilst in hospital was significantly associated with their infant feeding practices at 6 months. Thus, a woman who perceived to have a poor experience of BFHI practices in hospital was less likely to breastfeed compared to a woman who perceived her experience in hospital highly.

On analysis of results it was noted that one item was not worded in a way that allowed a true indication of 'exclusive' breastfeeding to be identified: the item failed to address the timing at which the child was given water. Consequently, the survey provides a population representative indication of 'full'

breastfeeding. Whilst there is debate over the importance of distinguishing between 'full' breastfeeding and 'exclusive' breastfeeding in developed nations, the Australian national key indicator is for 'exclusive' breastfeeding. Thus, mothers will be called back to gain information on when they first introduced water to the infant so that an indication of exclusive breastfeeding can be obtained.

This call back will occur during March and final data will be received in May 2011. The second phase of the survey will take place in 2012 to allow an evaluation of the roll out of the BHFI policy.

Funders of the project: Western Australian Department of Health.

#### DIABETES IN PREGNANCY: FACTORS AFFECTING COMPLIANCE WITH TREATMENT AND MANAGEMENT REGIMES FOR GESTATIONAL DIABETES MELLITUS (GDM)

Tracy Reibel, Janet Hornbuckle, Marina Mickleson, Rhonda Bradley, Cindy Porter, Marjorie Cameron.

This qualitative research project aims to profile women's perceptions of GDM and their views of the barriers and enablers to self-directed management of GDM. The information will assist in the development of strategies for clinicians to more effectively support women diagnosed with GDM to comply with recommended management approaches (principally diet, exercise and medication regimes). It is intended that the outcomes of the project will directly impact on service delivery to better meet the needs of women with GDM in all antenatal services.

This research aims to profile women's perceptions of GDM and their views of the barriers and enablers to self-directed management of GDM. The information will assist in the development of strategies for clinicians to more effectively support women diagnosed with GDM to comply with recommended management approaches (principally diet and

exercise regimes). It is intended that the outcomes of the project will directly impact on service delivery to better meet the needs of women with GDM in antenatal services across the state.

Indepth interviews with women diagnosed with GDM and with no pre-existing diabetes have been completed; with a total of 22 eligible women have been included in study. Clinical data is currently being collected and collated. Interviews have also been conducted with a number of clinicians at three of the four study sites. Analysis of interview transcripts is being undertaken and the Project Reference Group will meet in February, 2011 to finalise the outcomes for inclusion in the final report.

It is anticipated that this project will be completed by April 2011.

Funders of the project: Western Australian Department of Health

#### INNOVATIVE HEALTH SERVICES FOR HOMELESS YOUNG PEOPLE EVALUATION

Tracy Reibel, Tanyana Jackiewicz and Alicia Watkins

In Australia, Innovative Health Services for Homeless Youth Program (IHSHY) has developed a range of innovative service models that deliver health care to highly marginalised young people. IHSHY services in Western Australia (WA) target young people at high risk aged between 12 and 25 years. This qualitative research project aims to construct a profile of the attributes of these services that enable them to work successfully with marginalised young people with complex needs, including Aboriginal young people; and report on recommendations for these and other community based services that can better meet the needs of this target group. Five services across the Perth Metropolitan area were included in the study and these included: Fremantle StreetDoctor, Perth StreetDoctor, Hills Community Support

Service, Adolescent Mothers Support Service and the RUAH Young Women's Program.

The evaluation included interviews with clients of the five services that asked questions about their personal experiences with the service, their perceptions and their suggestions as to the future of IHSHY services and other community based services. We have also interviewed the deliverers of the services, who are partners in the research, to gain their perspectives on why they think their IHSHY service is effective in reaching this target group and the future of services to young people. This research project has made a commitment to incorporating a philosophy of doing research with young people rather than to young people by ensuring that those involved in the study are provided with some benefit for their involvement.

We have completed interviews with all the service providers (a total of 17 clinicians) and we have interviewed 42 clients from all 5 services. Numerous attempts were made at recruiting more clients for this study, however, we have been unsuccessful and will continue to do fieldwork until we have completed another 10 interviews with the Fremantle StreetDoctor clients. We have developed a results framework from the data collected to date and developed a model for service delivery. We are currently framing the theoretical underpinnings to this model and will input data from subsequent interviews into this model.

The preliminary results of this study were presented at the International Conference for Youth Studies in Glasgow in September 2010 and at the International Qualitative Health Conference in Vancouver in October 2010. The preliminary results were also presented in November 2010 to the Child and Youth Research Symposium.

This project is expected to be completed by April 2011.

Funders of the project: Western Australian Department of Health

## AN EVALUATION OF THE IMPLEMENTATION AND DISSEMINATION PROCESSES FOR THE WESTERN AUSTRALIAN OPERATIVE DIRECTIVE FOR CO-SLEEPING

Dr Jenny Dodd

This project will evaluate the implementation and dissemination processes of the Western Australian Department of Health's Operative Directive of co-sleeping (2008) (the directive) to investigate:

- What processes health services have in place to implement and disseminate the directive including: information, professional development and education for health workers and the information and educational resources made available to women.
- The understanding of health professionals about the directive; how do they interpret and respond to the recommendations in their every day practice;
- How health professionals respond to the concerns of parents who wish to optimise the likelihood of skin to skin contact and successful establishment of breast feeding in light of the directive's recommendations;
- What information women receive about the directive, how do they interpret and respond to it (in hospital and on discharge) and what they understand about it (including cultural appropriateness for Aboriginal and CALD women); what (if any) concerns they have about the information and education they are given.

Research and administrative activities on this project have included the preparation of a full scientific protocol and submission of ethics committee applications including: King Edward Memorial Hospital Ethics Committee (submitted, considered and final approval pending), WA Country Health Services (submitted, considered and approved), Child and Adolescent Community Health (submitted, considered and approved), WA Aboriginal Health Information and Ethics Committee (submitted in November, 2010).

Additional preparation for this project has included a presentation at the Women and Newborns Symposium in November, presentation and consultation with the Aboriginal Collaboration Council Advising on Research and Evaluation (ACCARE), and the presentation and consultation with the Aboriginal Maternity Support Services Unit.

A sample frame for the audit surveys for this project has also been developed and letters of invitation, information sheets about the project have been prepared for health professional and client research participants (pending approval from all ethics committees). A comprehensive literature review has also been completed and will be disseminated for review and comment to the Aboriginal Collaboration Council Advising on Research and Evaluation and the Project Reference Group.

Finally, a sample of 1064 WA women with 9 month old children will be asked questions in regard to co-sleeping to obtain a population estimate of co-sleeping in Western Australia. This will be completed by May 2011.

Funders of the project: Health Department of Western Australia

## TO INVESTIGATE THE RESOURCES AND SUPPORT AVAILABLE FOR WOMEN (INCLUDING ABORIGINAL AND CALD) ACCESSING MATERNITY SYSTEM SERVICES, WHO ARE AT RISK OF DOMESTIC VIOLENCE.

Dr Jenny Dodd

This research project will review and map the current processes, guidelines and protocols responding to pregnant women, at risk of domestic violence, who are accessing maternity system services in Western Australia. The referral pathways that are utilised will be identified through analysis of guidelines and protocols used by a range of maternity health system services and through interviews with Health professionals/workers and Social workers. Health professionals/workers and Social workers in maternity health

system settings who care for pregnant women (particularly Aboriginal and women from CALD communities) will be recruited to discuss the barriers and facilitators to providing services to pregnant women and babies and to identify resources, service models and professional development needs to respond appropriately to Aboriginal women and women from CALD communities. Professionals and support workers from the community and non-government sectors will also be included to identify the extent and efficacy of referral pathways from health services to a range of community, welfare and housing services in the non-government sector.

A full scientific protocol (and submission of ethics committee applications including: King Edward Memorial Hospital Ethics Committee (submitted, considered and approved), WA Country Health Services (submitted, considered and approved), Child and Adolescent Community Health (submitted, considered and approved) and WA Aboriginal Health Information and Ethics Committee (submitted in November, 2010).

Additional activities include the presentation and consultation with the Aboriginal Collaboration Council Advising on Research and Evaluation (ACCARE), and presentation and consultation with the Aboriginal Maternity Support Services Unit (AMSSU) within Womens and Newborns Health Service. Dr Dodd has also met with ISHAR multicultural women's health centre, Joondalup Women's Health Works and the Domestic Violence Advisory Service for guidance about research directions and questions.

A comprehensive literature review has also been completed and has been disseminated for review and comment to the Aboriginal Collaboration Council Advising on Research and Evaluation (ACCARE) and the Project Reference Group. Currently the researcher is updating the literature review with respect to changes in domestic violence and child protection law.

Funders of the project: Health Department of Western

Australia

### DELIBERATE SELF HARM IN WESTERN AUSTRALIA

Grant Smith, Tanyana Jackiewicz

(Previously Youth Suicide in Western Australia; project focus changed following scoping of research possibilities and after discussion with members of the Child and Youth Health Network)

Each year in Western Australia, there is a high number of admissions to emergency departments (EDs) for injuries caused by deliberate self-harm (DSH). The treatment of these injuries exerts a considerable burden on the WA health system. Despite the fact that protocols have been established for the assessment of risk for DSH ED patients and for the referral of these patients to psychiatric, counselling, and social services, a significant portion of these clients will be readmitted for DSH-related injuries. Prevention of readmission through more effective treatment/referral system may result in substantial savings to the WA health system.

This project will use qualitative and quantitative methods to examine the effectiveness of the various referral pathways (on separation from EDs) with regard to reducing the likelihood of readmission. The qualitative element of the project will involve interviews with first-time DSH ED clients and clients who have been admitted to ED for DSH injuries multiple times. Elements of the referral pathway that were helpful and those that were not helpful in preventing further episodes of DSH will be identified. The quantitative aspect of the project will involve the collection of data on referral pathways data from the written ED records of DSH clients. This data will be linked to Data provided by the Developmental Pathways Project (specifically the WA Emergency Department Data Collection, the Hospital Morbidity Data Collection, and Mortality) to determine which referral pathways are associated with a lower likelihood of repeat DSH admission (or suicide).

At this stage, support has been sought from hospitals with EDs in the Perth Metropolitan area. The majority of these have agreed to take part in the research following approval of the projects by Human Research Ethics Committees. The applications for ethical review will be submitted to the Princess Margaret Hospital Scientific Advisory Sub-Committee and will be under review by the Human Research Ethics Committee at their first meeting of 2011.

Both aspects of the project rely on receipt of linked data through the Developmental Pathways Project at the Telethon Institute for Child Health Research. Our expression of interest has been approved by their governance group; however, this data will not be available until July 2011.

Following receipt of the DPP data, linkage to the newly gathered data from the ED records will take approximately 6-8 months through the WA Data Linkage Unit. Given the time taken for data receipt and linkage, it is expected that this project will be completed by December 2012.

Funders of the project: Health Department of Western Australia

### CHILD AND ADOLESCENT COMMUNITY HEALTH (CACH) EVALUATION PROJECT

Tanyana Jackiewicz, Rachel Skoss.

This project involved the provision of research support to CACH planning and service delivery models at the level of child health and school health nurses.

TICHR has assisted CACH in providing critical reviews of the evidence relating to programs delivered by child and school health nurses for antenatal education and toddler parenting groups. In 2010, TICHR facilitated one workshop with service deliverers to discuss the evidence as well as facilitate a shared understanding of the role of child and school health nurses in these areas.

This project is now complete.

Funders of the project: Western Australian Department of Health.

## Motherhood after Migration

### THE PREGNANCY AND POSTPARTUM EXPERIENCES OF WOMEN FROM AFGHANISTAN, BURMA, CHINA, SUDAN AND VIETNAM

Brilliana Von Katterfeld.

The data collection for this PhD project was funded by the Women's and Newborns Health Network. Pregnancy is a time when many immigrant women can feel particularly vulnerable. Foreign-born women, especially those from CALD backgrounds, may be more likely to face problems navigating the local maternity health system, have issues with language and communication, deal with potential conflict between their traditional practices and those of the receiving country, and face social isolation, particularly when separated from extended family members who reside in the natal country or elsewhere.

This project explored the pregnancy and postpartum related experiences of CALD immigrant women who have given birth in Western Australia (WA) between 2004 and 2009. Information was gathered through focus groups, co-interviews and individual interviews with refugee women from Afghanistan, Burma and Sudan and free settlers from Vietnam and China. The report includes a number of recommendations for the improvement of perinatal care services for women from the targeted groups, as well as women from CALD backgrounds in general. A total of 39 women participated in the study.

All participants had experienced between one and seven pregnancies, not all occurring in Western Australia. Time since arrival in Australia varied from 8 months to 16 years. All of the women from Afghanistan, Burma and Sudan had

arrived as part of the federal government's Humanitarian Program. All of the women from China and Vietnam, except one, had entered on a student or skilled worker visa. One Vietnamese woman had entered on a family reunion visa, 10 years after two of her older siblings had entered Australia as refugees. In general, the women from China and Vietnam were highly educated. By comparison the refugee women had limited literacy in both English and their native language/s. There were high levels of fertility among both the Sudanese and Afghan women, especially noting that several of the participants were still of reproductive age and did not consider their childbearing to be over. Religious backgrounds varied with participants reporting to be Christian, Buddhist, Muslim or to have no religious affiliation.

Cultural and linguistic diversity is part of modern Australian society. Greater emphasis is currently being placed on providing appropriate and sensitive care for CALD populations. Pregnant women who have migrated to Australia are particularly vulnerable and deserving of equitable and culturally appropriate care. This study helps to highlight several areas where the pregnancy and postpartum experiences of CALD women are often different from the mainstream population. While this report has made recommendations for CALD women in general, it must be acknowledged that CALD groups are not homogeneous. The perinatal experiences of women from the same country of origin are influenced by multiple factors including time since arrival in Australia, education and employment, English language proficiency, economic resources, family structure and acculturation. This project has highlighted those areas where practical changes may be instigated by the health care system for the general benefit of immigrant women from CALD backgrounds, using the real life experiences of women from Afghanistan, Burma, China, Vietnam and Sudan as references.

Funders of the project: Health Department of Western Australia

### BIRTH OUTCOMES ASSOCIATED WITH ALCOHOL RESTRICTIONS IN THE FITZROY VALLEY

Grant Smith and Tanyana Jackiewicz

The damaging effects of excess maternal alcohol consumption during pregnancy on fetal development have been well documented. Maternal alcohol-use can prevent fetal absorption of nutrients, damage the developing nervous system, and can restrict the amount of oxygen provided to the fetus. These effects can result in Fetal Alcohol Spectrum Disorders (FASD), growth restriction (weight, length, head circumference), and birth defects. Children affected by alcohol in utero are also at risk of long-term difficulties, such as cognitive, social, emotional and behavioural problems.

Given the risk of poor outcomes for children affected by alcohol consumption in utero, the prevention of alcohol consumption at dangerous levels during pregnancy is of paramount importance. Fitzroy Crossing community members noted that an outcome they desired from the alcohol restrictions was the reduction of dangerous drinking during pregnancy and the subsequent improvement the outcomes for the next generation of children born in the area.

The aim of this research project is to determine whether the introduction of the alcohol restrictions were associated with improvements in select birth outcomes for children born to mothers residing in Fitzroy Crossing. The outcomes that will be measured are restricted to those available within the WA Midwives Notification Register. These include growth measurements, status at birth and pregnancy/birth complications. Long-term outcomes such as social, emotional and behavioural outcomes and those that require diagnosis during childhood (i.e. FASD) cannot be examined without purpose-designed longitudinal research.

It is hypothesised that growth measures will have improved for children born to Fitzroy Crossing mothers following the introduction of the alcohol restriction. A natural experimental design will be employed. Measures of birth outcomes for

Fitzroy Crossing singleton children born in the two years prior to the introduction of the alcohol restrictions (from October 1 2005 to September 30 2007) will be compared to Fitzroy Crossing singleton children conceived in the two years following the introduction of the restrictions (i.e. born from July 1 2008 to June 30 2010).

The results of this research will inform strategies to reduce the level of damage caused by fetal exposure to alcohol, improving the quality of life of the child and family and increasing the productiveness of the child to society. These benefits, taken in consideration with the fact that all data provided to researchers will be de-identified, indicate that the benefits of the research substantially outweigh any issues regarding privacy.

The research team is currently awaiting ethics approval and the subsequent receipt of data.

Funders of the project: Nindilingarri Cultural Health Services.

## Suicide Prevention

### SUICIDE PREVENTION RESEARCH AND TRANSLATION PROJECT

Shawn Phillips, Deborah Robertson, Kate Miller, Kim Adey, Nikki George, Stephen Zubrick.

The Institute's program of translational research in suicide prevention aims to ensure current policy and practice for the prevention of suicide and suicidal behaviour is informed by current scientific knowledge. The Institute also provided a secretariat for the Ministerial Council for Suicide Prevention up to 30th June 2010. The Council reports to the Minister for Mental Health.

In September 2009, the Ministerial Council for Suicide Prevention was re-convened with a new membership, the WA State Suicide Prevention Strategy 2009-2013 was launched

by the Minister for Mental Health and Expressions of Interest were called to manage the implementation of the \$15 million Strategy. TICHHR was selected as the Preferred Provider to manage the implementation of the Strategy but was not able to negotiate a satisfactory agreement with the Mental Health Division and the Ministerial Council for Suicide Prevention regarding the particulars of the business plan. As a result the twenty year study of completed suicides in WA has come to an end and the award winning Gatekeeper Suicide Prevention Training program for professionals has also been discontinued.

Funders of the project: Mental Health Division, Western Australian Department of Health.

#### **INTEGRATED PROACTIVE SUICIDE BEREAVEMENT POSTVENTION PROJECT**

Brian English, Shawn Phillips, Sharon Hillman, Larina Bromley, Phil Riseborough, Kristy Staples, Karen Ugle, Belle Glassen, Stephen Zubrick.

The ARBOR (Active Response Bereavement OutReach) Project has been extended to 30 June 2011 to enable a more comprehensive longitudinal study of the impact and outcomes of the services provided for those bereaved by suicide in the Perth Metropolitan area. The service offers Peer Support (volunteers bereaved by suicide who are trained to support those newly bereaved), short term counselling, home visits and groups. Evaluation of the service is being undertaken by Edith Cowan University with a comprehensive plan of evaluating the interagency collaborations that assisted in the development and delivery of the service, qualitative and quantitative data collection on wellbeing outcomes of clients and evaluation of the impact of being involved in the service for the Peer Supporter volunteers. Negotiations are underway to transfer the management of ARBOR to a suitable auspice with a focus on service delivery.

Funders of the project: Commonwealth Department of Health and Ageing.

### **Developmental Pathways in WA Children Project**

The Developmental Pathways in WA Children Project is a landmark project taking a multidisciplinary and holistic approach to investigate the pathways to health and wellbeing, education 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 the 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 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, well-being and development of children and

youth, their families and their communities.

Funders of the project:

The Developmental Pathways in WA Children Project was made possible by the generous cash and in-kind contributions made by all of the collaborating organisations and government departments, which was matched by the Australian Research Council (ARC) through 2 ARC Linkage Project Grants.

Sub projects within the Project

The Developmental Pathways in WA Children Project supports several postgraduate students, 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 PROTECTION THEME: CHILD ABUSE AND NEGLECT** Melissa O'Donnell.

Melissa O'Donnell is 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 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. Dr O'Donnell's current research includes WA Emergency Department presentations related to child maltreatment and intentional injury, mental health admissions of parents related to children who have contact with the child protection system. She is also undertaking two international collaborations: international comparisons of child abuse and neglect indicators using hospital morbidity, mortality and child

protection data (UK, USA, Manitoba, NZ, Sweden) with Prof Ruth Gilbert, and international comparison of trends in acute injury hospital admissions related to child maltreatment (UK and WA).

## **SOCIAL DETERMINANTS THEME: SOCIAL DETERMINANTS OF HEALTH**

Amanda Langridge.

Dr Langridge's research investigates social and racial inequalities in various child health and developmental outcomes in Western Australia. It utilises longitudinal, administrative data from the WA Government Departments of Health, Education and Child Protection to examine trends over time, as well as identify child, parental and community-level factors that influence these outcomes. It is anticipated that findings from this research will provide a method by which inequalities can be monitored using routinely collected administrative data to best inform Government policies and practices that seek to minimise these inequalities. Dr Langridge is currently looking at the following research areas: developing a proxy individual-level socioeconomic indicator from routinely collected administrative data, parental education and children's educational attainment, paternal characteristics and poor fetal growth, and social and racial inequalities in infant mortality. She is also collaborating with international researchers from Edinburgh, Glasgow, Sweden, Denmark, Norway, Massachusetts, and California on a descriptive study of trends in pregnancy hypertension and preeclampsia in high income countries.

## **DO YOU SEE WHAT I SEE? AN EXPLORATION INTO THE DELIVERY OF HEALTH, EDUCATION AND CHILD PROTECTION SERVICES BY THE WA STATE GOVERNMENT TO ABORIGINAL CLIENTS IN THE PERTH METROPOLITAN AND GERALDTON REGIONS**

Glenn Pearson.

This qualitative research 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 receiving of these services.

## **ON THE DIMENSIONS AND DEVELOPMENT OF JUVENILE DELINQUENCY: A POPULATION-BASED STUDY OF THE PREVALENCE AND FREQUENCY OF OFFENDING AND THE INFLUENCE OF INDIVIDUAL, FAMILY AND COMMUNITY FACTORS ON DELINQUENCY IN WESTERN AUSTRALIAN CHILDREN**

Anna Ferrante.

The aim of this 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.

## **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**

Jocelyn Jones.

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.

## **RISK FACTORS AND OUTCOMES FOR CHILDREN WITH ATTENTION DEFICIT DISORDER (ADHD) TREATED ON STIMULANT MEDICATION IN WESTERN AUSTRALIA: USING LINKED POPULATION DATA SOURCES AND A DETAILED QUESTIONNAIRE.**

Dr Desiree Silva.

ADHD is the most common neurodevelopment disorder affecting 6-10% of children worldwide with well known clinical consequences and functional outcomes that can affect individuals throughout their lifespan. Despite extensive research in this field there appears much controversy around the aetiology, diagnostic methods, clinical outcomes, treatment and management of children with this disorder. There is much debate on the use of stimulant medication (SM) and its outcomes which have not been examined at a population level. This study aims to identify:

- Potential antenatal and early neonatal risk factors associated with children requiring treatment with SM in WA.
- Hospital and emergency morbidity, accident related hospitalisation risk, criminal and anti social behaviour, and service needs associated with children on stimulant treatment for ADHD.
- Education outcomes of children diagnosed with ADHD and their level of SM treatment over the testing period.
- The mental health burden of parents and family functioning of children diagnosed and treated with pharmacotherapy for ADHD in WA.

## **THE RELATIONSHIP BETWEEN EDUCATIONAL AND MENTAL HEALTH OUTCOMES FOR WESTERN AUSTRALIAN CHILDREN: A LONGITUDINAL POPULATION STUDY**

Janice Wong.

A major and important contributing variable to children's

wellbeing is their mental health. 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. Development of mental health issues in childhood may have serious consequences in adulthood. This study aims 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. This study will provide a better understanding of how environmental, and dependent variables interact together. 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.

## Human Capability

### MEASURING AND MODELLING THE CHILDHOOD DETERMINANTS OF HUMAN CAPITAL FORMATION AND HUMAN CAPABILITY EXPANSION

Stephen Zubrick, Sven Silburn, Dennis Trewin, Ann Sanson, Bill Loudon, 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 aims to integrate archival data with population data registers in the health, education and social services sectors to study patterns of participation (or non-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. Key research findings

this year include:

- teenage pregnancy was found to be significantly associated with family type, highest school year completed by primary carer, combined carer income, whether the primary carer was a smoker and whether the girl displayed aggressive and delinquent behaviours during childhood and adolescence. Aggressive and delinquent behaviours were predictive of teen pregnancy even when observed at young ages.
- deliberate self-harm was found to be significantly associated with female sex, primary carer being a smoker, being in a step or blended family, having more emotional or behavioural problems than other children, living in a family with inconsistent parenting style, and having a teenage mother.
- using data from the Longitudinal Study of Australian Children we studied the interaction between parenting styles and children's temperaments. Results were presented at the International Society for the Study of Behavioural Development conference in Zambia in July.
- people with common mental disorders such as anxiety or depression smoke at substantially higher rates than the remainder of the community, and represent about one-third of Adult smokers in Australia. People with these disorders are more likely to start smoking, less likely to quit, and smoke on average for longer duration, despite wanting to quit and trying to quit as much as anyone else. These people are less able to respond to the mainstream anti-smoking campaigns that have been successful in the broader population.
- Using data from the WA Aboriginal Child Health Study we examined the impact of maternal death on the onward psychosocial circumstances of Aboriginal children and young people. Although the death of a birth mother is relatively rare and the vast majority of Aboriginal children

with adverse developmental outcomes live in families and are cared for by their birth mother, we found that the loss of a birth mother and the circumstances arising from this impart a level of onward developmental risk for mental health morbidity.

Funders of the project: Australian Research Council.

### CHILD AND ADOLESCENT COMPONENT OF THE NATIONAL SURVEY OF MENTAL HEALTH AND WELLBEING

Stephen Zubrick, Jennifer Hafekost, David Lawrence.

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, and the Institute is participating in sample design and content development work in preparation for a second national survey of children and young people.

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.

The development work for this study includes reviewing surveys of child and adolescent mental health and wellbeing internationally, reviewing relevant instruments and questionnaires in the field, and facilitating consultation with relevant stakeholders to help refine and articulate the goals for the survey. Methodological work to develop an appropriate sampling strategy to achieve these goals is also being undertaken. The work will also include emerging content areas relevant to the social and emotional wellbeing of children and young people including the impact of new and emerging technologies on peer relations and bullying

behaviours, and the role of social inclusion in fostering emotional wellbeing.

Funders of the project: Australian Government Department of Health and Ageing.

## Australian Early Development Index

Stephen Zubrick, Sally Brinkman, Sven Silburn, Sharon Goldfeld, Frank Oberklaid, Mary Sayers.

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

The AEDI is based on the Canadian Early Development Instrument (EDI) which was developed by Dr Janus and Dr Offord at the Offord Centre for Child Studies, Mc Master University. In Australia, the Canadian EDI checklist was first trialed in the northern metropolitan suburbs of Perth in 2002 and 2003, with around 4,300 children. Since 2004 the adaption of the EDI - now called the Australian EDI, or AEDI has been carried out by the Centre for Community Child Health in partnership with the Telethon Institute for Child Health Research.

The Telethon Institute for Child Health Research has been

primarily responsible for the technical adaptation and the scientific research and analyses of the development of the AEDI in Australia. A major piece of work has included the Indigenous adaptation of the AEDI with a focus not just on the checklist itself but the associated teacher guidelines and the dissemination of AEDI results in Indigenous communities. The Indigenous AEDI adaptation study is jointly funded by Shell Australia and the Department of Education, Employment and Workplace Relations (DEEWR).

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. Between 1 May and 31 July, information was collected on 261,203 children (97.5 per cent of the estimated national five-year-old population). This involved 15,528 teachers from 7423 Government, Catholic and Independent schools around Australia. The initial results (released in December 2009) provide a snapshot of the early childhood development outcomes for children in communities across Australia. In 2010 small area localities were repeated to enable geographical mapping. Schools that didn't participate in 2009 were also able to participate in 2010. The final release of the AEDI results are likely to be released in April/May 2011.

Funders of the project:

The AEDI is conducted by the Centre for Community Child Health (at The Royal Children's Hospital, Melbourne and a key research centre of the Murdoch Childrens' Research Institute) in partnership with the Telethon Institute for Child Health Research, Perth. The national implementation of the AEDI is funded by the Australian Government Department of Education, Employment and Workplace Relations.

## Early Child Development, Program Evaluation:

### RANDOMISED CLUSTER CONTROL TRIAL EVALUATING THE IMPACT OF AN EARLY CHILDHOOD EDUCATION AND DEVELOPMENT INITIATIVE ACROSS INDONESIA

Sally Brinkman, Menno Pradhan, Amanda Beatty, Amelia Maika, Elan Satriawan.

With a greater scale for improvement in school readiness outcomes, the evaluation of ECED programs in the 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.

With significant economic growth over the last 5 years, Indonesia is currently classified as a lower to middle income country. Despite this fact, there are over 35 million people living below the poverty line – representing 16% of the population. In addition it is estimated that up to half the 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 Early Childhood Education and Development program 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/caretakers living in about 6,000 poor communities (dusuns) located in 3,000 villages within 50 districts. Participating districts have been selected according

to poverty level and their commitment to developing ECED services.

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. It is essential that the research will be able to determine what factors contributed to any success or failures by the ECED program. 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 ADRA Grant has enabled the employment of two early career academics based at the University of Gadjadara (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. There is a clear and recognised deficit in Indonesia in the knowledge and capacity regarding high quality research methods, research application, instrument development, statistical/analytical skills and the importance of good quality evaluations of programs (such as this ECED program) as well as simply a lack of understanding of the importance of early child development and education. Building local capacity will decrease the current reliance on "fly-in consultants". Over the time of this research our aim is to ensure that Dr Elan Satriawan and Ms Amelia Malika will independently have

the skills, knowledge and confidence to be able to design, undertake and manage such large scale research programs and have the confidence to disseminate the research findings to government, donors and other stakeholders including within the academic literature.

Funder of the project: Australian Development Research Award (ADRA) awarded by AusAid.

#### INTERNATIONAL CONSORTIUM FOR THE MONITORING OF CHILD DEVELOPMENT.

Sally Brinkman, Clyde Hertzman, Magdalena Janus, Fraser Mustard, Mary Young.

As international interest and acknowledgment grows around the importance of monitoring child development various countries are looking for support in initiating monitoring activities. As such an International Consortium for the Monitoring of Child Development has been formed between the Offord Centre at McMaster University and the Human Early Learning Partnership in Canada along with the Telethon Institute for Child Health Research and the Centre for Community Child Health in Australia, with the WorldBank as a partner organisation. Currently the Institute for Child Health Research is involved in supporting Indonesia, Argentina, Scotland, the United Arab Emirates and Peru in their endeavors to adapt the EDI.

Funders of the project: Supported by: WorldBank, Van Leer Foundation and UNICEF.

## LOOKING at Language

Mabel Rice, Kate Taylor, Stephen Zubrick, Shelley Smith.

LOOKING at Language is a 10-year study (2002 – 2012) of language development and disorders in twins and singleton children funded by the National Institutes of Health (NIH). The study, known as LOOKING at Language, is an international collaboration between Professor Mabel Rice from the University of Kansas, Associate Professor Kate Taylor and Professor Stephen Zubrick from the Centre for Developmental Health and Professor Shelley Smith from the University of Nebraska Medical Center. We are investigating genetic and environmental influences on normal and impaired language acquisition in 1000 WA twin and singleton children at 2, 4, 6 and 9 years. Our focus is on possible genetically guided developmental timing effects, such that inherited mechanisms activate or are delayed at developmental transition times, across different dimensions of language, across language and reading phenotypes. The outcomes will be highly relevant for the identification of children at risk for language disorders and the estimation of possible genetic, environmental, and interactive age modulated effects on language acquisition and impairment and reading acquisition and impairment. Our early publications have shown that early language delay is governed far more by basic biological processes and process internal to the child than it is by environmental circumstances. We established that one in five children with early language delay are at risk for language impairment at 7 years and that syntax and morphosyntax are the most vulnerable aspects of language for children with a history of early language delay. We are set to realize the publication opportunities from this study over the next few years when data from successive birth cohorts is available from each wave of follow-up (i.e., 2, 4, 6 and 9 years). The study provides a unique multidimensional population based longitudinal dataset for studying language acquisition, Specific Language Impairment, reading acquisition and reading impairment.

Funders of the project: U.S. National Institutes of Health.

## The Western Australian Pregnancy Cohort (Raine) Study

The Raine Study is a cohort of children born in Western Australia between September 1989 and April 1992 who have been followed closely over the last 20 years by a collaborative team of researchers from The Telethon Institute for Child Health Research, The University of Western Australia (Schools of Women's & Infants' Health and Medicine & Pharmacology), Curtin University and the University of Notre Dame. The Raine Study is one of the largest successful prospective cohorts of pregnancy, childhood and adolescence to be carried out anywhere in the world. The Raine Study is based at TICHR and is an invaluable asset to Western Australian Researchers. The Raine Study is governed by the Raine Study Executive Committee. Day to day running of the cohort and data collection is managed by the Raine Study Manager and the Study Team. There are over 20 research groups utilizing the Raine Study Cohort data. There is growing collaborative research between Raine Study Principal Investigators. Further, national and international collaborations with the Raine Study are continuing to develop and add value to the cohort and expand research opportunities. 2010 saw the cohort members begin to turn 20, and participate in the 20 year follow up of the cohort. This is the thirteenth time point where data has been collected on the cohort.

Core Management funding:

The Telethon Institute for Child Health Research

The University of Western Australia

Raine Medical Research Foundation, UWA

UWA Faculty of Medicine, Dentistry and Health Sciences

Women and Infants Research Foundation

National Health and Medical Research Council of Australia

National Heart Foundation

Rotary Health Research

Canadian Institute of Health Research

Scientific Director: Craig Pennell

Study Manager: Jenny Mountain

Data Manager: Louise McKenzie

Team Leader: Diane Wood

Raine Study Team:

Jenny Mountain, Louise McKenzie, Diane Wood, Alex Baptista, Tegan Grace, Emily Hockley, Natasha Larter, Jessica Hall, Sue Greene (phlebotomist), Amy Lee, Denny Craig, Carolyn Smargiassi

### THE RAINE STUDY 20 YEAR FOLLOW UP - THE RAINE EYE HEALTH STUDY: AN OPHTHALMIC FOLLOW-UP STUDY OF A LONGITUDINAL BIRTH COHORT AT AGE 20 / 21 YEARS

David Mackey, Alex Hewitt, Alla Soloshenko, Sandra Oates, Seyan Yazar, Craig Pennell, Jenny Mountain, Raine Study Team.

In 2010 the Raine Study commenced the follow up of the cohort participants at twenty years of age. The Raine Eye Health Study is examining eye health in an age group for which very little data exist. It is presumed that young adults have the best vision and thus very few people have studied people of this age group. The primary aims of this study are: (1) To document the prevalence of the eye conditions: refractive error, amblyopia and strabismus, in young adults; (2) To

determine the population distribution of endophenotypes/biometry related to eye diseases in young adults; (3) To determine genetic and early environmental factors that influence ocular biometry and predispose to ophthalmic disease; and (4) To investigate the interaction of early life, familial, lifestyle, demographic and genetic risk factors with these conditions, and their endophenotypes. Raine Study participants are invited to the Lions Eye Institute to undergo a comprehensive set of eye tests checking eye sight and vision and the health of the eyes. The results of all these tests are given to the participant during the follow-up, and where necessary glasses prescriptions or treatment are provided. In addition participants complete a questionnaire which includes information on sociodemographics, relationships, mental health, spinal pain, physical activity, asthma and atopy, risk taking behaviour and medical history, and the Cancer Council short food frequency questionnaire. Participants also have physical measurements (height, weight, anthropometry) and blood pressure testing.

During the assessment the participants have a DEXA scan, which measures body composition (fat mass, lean mass and bone density). Participants also provide a fasting blood sample at a domiciliary visit by the Raine Phlebotomist.

Funders of the project:

NH&MRC 634445, 634457, 634509, Canadian Institute of Health Research, Raine Core Management Funding

Australian Foundation for the Prevention of Blindness

Lions Eye Institute

### THE RAINE STUDY 20 YEAR FOLLOW UP - DEXA SCAN IN THE RAINE COHORT

Craig Pennell, Leon Straker, Raine Study Team.

Bone mineral content, body composition and percentage body fat are assessed from dual energy X-ray absorptiometry

(DEXA) scans. During the 20 year follow up visit, each Raine participant has a whole body DEXA scan using a Norland XR36 Quickscan machine. DEXA is the most widely used clinical tool for the assessment of skeletal integrity owing to its efficiency, precision and accuracy. The DEXA provides measures of body composition (lean mass, fat mass, bone mass) as well as bone density. The DEXA is considered the 'gold' standard measurement of adiposity.

Funders of the project: Canadian Institute of Health Research.

#### THE RAINE STUDY 20 YEAR FOLLOW UP - FIBROSCAN IN THE RAINE COHORT

Eng Gan, Leon Adams, John Olynyk, 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 major determinant of severity and outcome for NAFLD is the degree of hepatic fibrosis (tissue scarring in the liver). Assessment of fibrosis has traditionally required the use of a liver biopsy. However, due to its invasive nature and problems of sampling error, variability in interpretation and cost, non-invasive alternatives such as Fibroscan® (Echosens™, France) have recently been developed. A FibroScan fulfils many criteria required for non-invasive assessment of liver fibrosis. It is quick; taking on average five minutes, has good reproducibility, is most importantly, acceptable to the patient, and examines a relatively large sample of the liver. As part of the 20 year follow up, Fibroscan® is being used in the Raine cohort to non-invasively quantify hepatic fibrosis in the Raine cohort and establish norms in this age group.

Funders of the project: NH&MRC 634445.

#### RAINE STUDY 20 YEAR FOLLOW UP - THE EARLY LIFE ORIGINS

#### OF IMPAIRED TESTICULAR FUNCTION.

Roger Hart, Stephen Junk, Dorota Doherty, Michelle Pedretti, Raine Study Team.

Over the last few years there have been reports that male sperm counts are diminishing and that this is beginning to be obvious at a younger age. Many of these findings are based on sperm counts from people seeking infertility treatment, and not from healthy groups of people. It is not known why some people have low sperm counts. It may be through exposure to passive smoking, or early life events. Obesity is one of the factors that lead to a reduced sperm count, and it is believed that there might be other possible contributors in childhood health and diet. As a population we are being exposed to increasing amounts of chemicals in the environment (endocrine disruptors) which may have an effect. This study of male participants in the Raine Study cohort is the first study to utilise a large and well-established cohort prospectively followed from intrauterine life through adolescence into adulthood to investigate key fetal and childhood events leading to reduced semen parameters and decreased testicular volume. Recruitment began in April 2010, and results and clinical support are provided to participants.

Funders of the project: NH&MRC 634457.

#### RAINE STUDY 20 YEAR FOLLOW UP - EARLY INFLUENCES ON ADULT BEHAVIOUR AND THINKING STYLES

Andrew Whitehouse, Martha Hickey, Raine Study Team→

This study is examining autism-like behaviours in the general population to test the two most prominent biological theories of Autism Spectrum Disorders (ASDs), namely, that ASDs are caused by (1) early brain overgrowth, or (2) exposure to elevated levels of fetal testosterone. There is agreement that autism-like symptoms, including social and communication difficulties, are on a continuum in the general population, with Autism Spectrum Disorder (ASD) representing the

extreme end of the distribution. This study examines autism-like behaviours in the general population by requesting the Raine Study Cohort to complete a 50-item questionnaire measuring systematic (logical and organised) and empathetic (understanding and sympathetic) patterns of thinking. Raine Study participants are given the opportunity to either log onto the Raine Study Website with a unique identifier and password and complete the questionnaire online or to complete a paper copy. Measures of head circumference and fetal testosterone are available on the cohort from prenatal ultrasounds and cord blood.

Funders of the project: Research Funds from Prof Martha Hickey.

#### RAINE STUDY - "CHALLENGE ME" STUDY

Craig Pennell, Anke van Eekelen, Stephen Lye, John Newnham, Karen Bosel, Hilary Hii, Blagica Penova-Veselinovic, Krysia Zarzycki, Raine Study Team.

2010 saw the completion of the recruitment of the Raine Study Cohort at 18 years of age for the "Challenge Me" study. The study is the largest assessment of stress-induced hypothalamic-pituitary-adrenal (HPA) axis function ever conducted with over 1100 Raine study members participating. The results of this study will be evaluated together with previously collected data. The HPA axis impacts on hormonal function, growth, behaviour and brain maturation throughout childhood and adolescent.

Funders of the project: Canadian Institute of Health Research.

#### RAINE STUDY: DEVELOPMENTAL NEUROSCIENCE GROUP

Anke van Eekelen, Eugen Mattes, Jonathon Foster, Michael Smith, Raine Study Team

In 2010, 60 Raine Study participants underwent a functional magnetic resonance imaging (fMRI) scan. The 60 participants

from three groups previously tested for resting levels of cortisol (relatively low, medium or high) were invited to undergo an fMRI. fMRI outcome analysis enables the researchers to observe the brain function and investigate whether cortisol may have disrupted neurobiological processes of adolescent brain maturation. The cognitive ability of teenagers has been previously measured during the 17 year follow up when participants completed a 'cogstate' test.

Funders of the project: NH&MRC 458623.

## RAINE STUDY - GENETIC EPIDEMIOLOGY GROUP

Craig Pennell, Stephen Lye, Lyle Palmer, Lawrie Beilin, John Newnham, George Davey-Smith, Nicole Warrington, Qi Wei Ang, Louise Mckenzie.

Chronic disease is responsible for much of the burden of adverse health in Australia and other countries. Genetic epidemiology is the study of the determinants of complex disease, and in particular the role of genetics in these diseases. 2010 saw the completion of a Genome Wide Association Scan of the Raine Study participant's DNA. This resulted in access to 2.5 million genetic variants in over 1,500 Raine Study participants. The Raine Genetic Epidemiology group aims to identify genes that contribute to key developmental pathways in order to better understand the developmental origins of health and disease. The group collaborates with other large international genetics consortia, with include the Early Growth Genetics (EGG) consortium at the University of Oxford, and the EARly Genetics and Lifecourse Epidemiology (EAGLE) Consortium, at Erasmus University in The Netherlands. The EAGLE Consortium includes nearly all major birth and pregnancy cohorts with GWAS data internationally.

Funders of the project: NH&MRC 572613.

## CHILDHOOD DETERMINANTS OF RISKY SEXUAL BEHAVIOUR IN ADOLESCENCE: A PROSPECTIVE COHORT STUDY

Rachel Skinner, Martha Hickey, Eugen Mattes, Dorota Doherty, Anthony Smith, Susan Rosenthal, Spring Cooper, Michael Smith.

This research project aims to identify childhood factors which influence an adolescents' likelihood to initiate sexual activity at a young age, and engage in sexual risk taking. Risky sexual behavior contributes to unplanned teenage pregnancy, sexually transmitted infections (STIs) and adverse social, emotional and physical health outcomes in adolescence into adulthood. We have little understanding of early determinants of risky sexual behavior.

The Raine Study provided extensive biological, psychological, psychosocial, family, individual and environmental characteristics collected at all ages. This unique dataset is currently being utilised to undertake a world first analysis of causal pathways through early life to sexual risk-taking in adolescence.

Initial analyses show higher scores for Total Behavior Problems and the Externalizing Behavior subscale of the Child Behavior Checklist (CBCL) in participants who had already engaged in sexual intercourse compared to those who did not. In addition, participants who were identified with clinically recognized delinquent and aggressive behavioral problems at ages 5, 8, 10 and 13, were more likely to have engaged in sexual intercourse. These unique data indicating early predictors of risky sexual behavior in adolescence may help determine how and at what ages interventions may be effective.

Funders of the project: NH&MRC 634509

## EARLY LIFE STRESS, ADOLESCENT BRAIN DEVELOPMENT AND RISK FOR ADVERSE COGNITIVE AND PSYCHOSOCIAL OUTCOMES (THE RAINE STUDY)

Anke van Eekelen, Eugen Mattes, Jonathan Foster.

This project primarily aims to study early life stress and its association with HPA-functioning, cognition, and mental health during adolescence in the Western Australian Pregnancy Cohort Study (Raine Study). Our main hypotheses were that increased and sustained trajectories of early life stress and family dysfunction during childhood would increase the risk of Raine Study adolescents experiencing: a. increased HPA functioning, with i. higher baseline cortisol levels at 13 and 16 years of age, and ii. atypical cortisol response to physiological stress test at 13 years of age; b. increased HPA functioning at 13 and 16 years of age if they are carriers of specific haplotypes of the glucocorticoid and mineralocorticoid receptor genes; c. depression at 13 and 16 years of age if they are homozygous or heterozygous for the short allele of the serotonin transporter (5-HTT) gene; d. poorer cognitive performance on CogState testing at 16 years of age; e. atypical "non-prefrontal cortex (PFC)" brain activity during cognitive testing, as measured by fMRI at 16 years of age; f. more mental health problems at 13 and 16 years of age, as measured by the Child Behaviour Checklist (CBCL) and Beck's Depression Inventory.

Objective #1: Profiling of human HPA function in "Raine Study" adolescents at 16 years of age: In May 2009, we completed the collection of blood (n=1263) and saliva (n= 1150) in the Raine Study as part of the 16 year follow up. By June 2009, hormone analysis was completed on morning fasting plasma to reliably detect ACTH in 1257 Raine teenagers and total cortisol in 1259 Raine teenagers; the average free cortisol level in awakening saliva over 3 consecutive days was determined in 1150 Raine participants. All samples were measured in duplicate. These numbers represent approximately 71% of the Raine participants who took part in the 16-year follow-up of the Raine longitudinal study on Child Health and Development.

An integrated assessment of pituitary ACTH, adrenal total cortisol and free biologically active cortisol in each participant was used to determine basal HPA-activity at different levels of the axis. Linear regression modelling confirmed the expected theoretically driven correlation between these crucial intermediate and effector hormones of the stress-sensitive feed forward cascade of neuroendocrine events within the HPA-system. Gender-specific differences were also identified. Further use of the integrated HPA-outcome approach, rarely undertaken in relatively large cohorts like the Raine Study, allowed for the identification of specific HPA-related endophenotypes using derived HPA-outcome variables reflecting adrenal sensitivity to ACTH (determined by pituitary ACTH and adrenal total cortisol release in blood) and free cortisol. A manuscript on these outcomes was finalised for submission to an international peer-reviewed journal in 2010. This manuscript is now being revised for resubmission, with further blood profiling to be included. Manuscript preparation is also currently in progress with respect to significant influences of specific types of early life stress on HPA function at 16.

**Objective #2: Genotyping of each Raine Study participant.** Association analysis between the functional MR and GR SNPs and resting HPA activity in late adolescence has been finalized with no significant associations observed in this cohort. Using a systems biology based approach to candidate gene selection within the integrated network of stress-sensitive neurosignaling pathways in the brain, we have detected a polygenic effect of SNPs in the GR and 5HTT gene on depression-related behaviour. This is a novel finding which is accepted for publication (Van Eekelen et al., Aust J of Psychology (Special Issue) 2011).

**Objective #3: Testing of cognitive functioning with CogState at the age of 16.** Cogstate test data collection has also been finalized in May 2009 on over 700 participants, and association analysis with resting HPA outcomes and recently available mental health data at age 16 has been undertaken. Initial

analyses of the HPA and CogState data has indicated non-systematic relationships; however, we anticipate that further analyses will be undertaken in 2011 with respect to the 'Challenge Me' Study which has evaluated HPA functioning in direct response to a psychosocial stressor. fMRI testing, as initially proposed, started successfully in late 2009 and was completed by June 2010 (this was as agreed by NHMRC approval for an extension of this project grant to 31st December 2010). A total n=60 was completed for the fMRI project, which represents a large cohort for an fMRI study. Pre-processing of the fMRI data has been undertaken (indicative of group differences across the three levels of the Stroop task), and we are currently engaged in region of interest (ROI) data analyses.

Funders of the project:

NHMRC (2007-2010) Women and Infants Research Foundation of Western Australia (WIRF; 2006-2008)/ Canadian Institutes of Health Research (CIHR; 2007-2010), ARC/NHMRC Program Support for New Collaborations through ARACY/NGED networks 2008.

#### **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 aims to (i) determine the prevalence of eating disorders at two time points in adolescence, in a population-based cohort followed over time; (ii) identify factors that predict the persistence of eating disorders across adolescence; and (iii) identify prospective risk factors for early and later-onset adolescent eating disorders.

The research utilises data from the Western Australian Pregnancy Cohort (Raine) Study. Eating disorder questions were completed by 1,598 Raine Study participants at age 14 and 1,242 participants at age 16/17. Data at both time points

are available for 1,127 adolescents.

The prevalence of full and partial eating disorders, according to DSM-IV criteria, increased from 6% at age 14 to 9.5% at age 16/17. Of the participants with an identified eating disorder at age 14, 37% continued to meet criteria for an eating disorder at 16/17. An additional 9% ceased to meet diagnostic criteria but continued to experience sub-clinical eating pathology. Persistent eating disorder symptoms were associated with persistent difficulties in other areas (e.g., depression). Only 17% of the 14-year eating disorder group had been diagnosed with, or treated for, an eating disorder by age 16/17.

Findings from the project are expected to advance the small body of prospective research on risk and maintaining factors for eating disorders. The latter stages of the project will focus on translating research outcomes into practical strategies to facilitate effective prevention and early intervention efforts.

Funders of the project: National Health and Medical Research Council (NHMRC).

#### **RAINE STUDY: NUTRITION GROUP**

Wendy Oddy, Gina Ambrosini, Therese O'Sullivan, Monique Robinson,

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. 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 2010 the Nutrition Team were involved in the projects listed below:

## DIETARY INTAKE OF OMEGA-3 FATTY ACIDS AND RISK OF DEPRESSION IN ADOLESCENTS

Wendy Oddy, Siobhan Hickling, Michael Smith, Therese O'Sullivan, Monique Robinson, Nicholas de Klerk, Lawrie Beilin, Trevor Mori, Steve Zubrick, Sven Silburn.

This project examined the essential fatty acids in the diet and their effects on child mental health. Teenagers during the 14-year Raine Study follow up completed a Food Frequency Questionnaire (FFQ) to assess dietary fatty acid intake, as well as other nutrition intake at age 14. Fatty acids were assessed in a blood sample from the participants. Participants also completed the Beck Depression Inventory for Youth (BDI-Y) at age 14 and at age 17.

**Results.** An inverse relationship was observed between intake of both saturated fat and of n-3 PUFA at age 14 and BDI-Y scores at both 14 and 17 years of age. However, after adjusting for energy (kJ) intake and other lifestyle confounders, the relationships were no longer significant.

**Conclusions.** Associations previously reported between n3 PUFA and depressive tendencies may be due to collinearity with other dietary and lifestyle factors.

Funders of the project: Heart Foundation/ Beyond Blue Strategic Research Initiative grant.

## A LONGITUDINAL STUDY OF DIETARY RISK FACTORS FOR CARDIOVASCULAR DISEASE (METABOLIC SYNDROME) AND DEPRESSION IN ADOLESCENCE

Gina Ambrosini, Rae-Chi Huang, Trevor Mori, Beth Hands,

Therese O'Sullivan, Nick de Klerk, Lawrence Beilin, Wendy Oddy.

The nutrition team is investigating the association of dietary factors with metabolic and depressive outcomes in a longitudinal model using data from the Raine Study Cohort. In the first part of this project Dr Ambrosini investigated the effect of dietary patterns on metabolic risk factors.

Overweight and other risk factors for cardiovascular disease (CVD) as well as their clustering, or the metabolic syndrome, are increasingly prevalent among children and adolescents. We examined dietary patterns, CVD risk factors, and the clustering of these risk factors, in a group of 14 year olds living in Western Australia. To do this, usual dietary intake was assessed with a food frequency questionnaire. Two dietary patterns, 'Western' and 'Healthy', were identified using factor analysis. Associations between these dietary patterns and BMI, waist circumference, systolic blood pressure, fasting levels of serum glucose, insulin, total cholesterol, HDL C, LDL C, triglycerides and insulin resistance were assessed using analysis of variance. Belonging to a high risk cluster for these risk factors was examined in relation to dietary patterns using logistic regression. Aerobic fitness and socio demographic factors were considered as potential confounders. Our results showed that 1,139 adolescents provided complete data. Higher 'Western' dietary pattern scores were associated with a greater odds of belonging to the high risk cluster (p for trend =0.02) and greater mean values for total cholesterol (p for trend=0.03), waist circumference (p for trend=0.03) and BMI (p for trend =0.02) in girls, but not boys. Scores for the 'Healthy' dietary pattern were not related to the high risk cluster but were inversely associated with serum glucose in boys and girls (p for trend=0.01 and 0.04 respectively) and were positively associated with HDL C in boys (p for trend=0.02). From this project we concluded that dietary patterns were associated with CVD risk factors and the clustering of these risk factors in adolescence.

Funders of the project: Heart Foundation/ Beyond Blue Strategic Research Initiative grant.

## POLYUNSATURATED FATTY ACID INTAKE IS INVERSELY ASSOCIATED WITH BLOOD PRESSURE IN ADOLESCENT BOYS

Therese O'Sullivan, Alexandra Bremner, Lawrie Beilin, Gina Ambrosini, Trevor Mori, Rae-Chi Huang, Wendy Oddy.

Dietary intake of fatty acids, particularly omega-3 fatty acids, may modify blood pressure, however the evidence is generally limited to middle-aged or hypertensive populations. The aim of this project was to examine cross sectional associations between blood pressure and fatty acid intakes in adolescents participating in the 14-year follow-up of The Western Australian Pregnancy Cohort (Raine) Study. Fatty acid intakes were assessed in 814 adolescents aged 13-15yrs using 3-day diet records and an updated fatty acid food composition database. Resting blood pressure was determined using multiple readings. In adjusted regression models, systolic blood pressure was inversely associated with intakes of total polyunsaturated (b=-0.436, P<0.01), omega-3 (b=-2.47, P=0.02), omega-6 (b=-0.362, P=0.04), and long chain omega-3 fatty acids (b=-4.37, P=0.04) in boys. Diastolic blood pressure and mean arterial pressure were inversely associated with intakes of long chain omega-3 fatty acids in boys only (b=-3.93, P=0.01, b=-4.05, P=0.01, respectively). For specific long chain omega-3 fatty acids, significant inverse associations were observed between eicosapentaenoic acid and docosahexaenoic acid with measures of blood pressure, but no significant associations were observed with docosapentaenoic acid. No significant associations were observed in girls, or with the omega-6 to omega-3 ratio. In conclusion, higher intakes of both omega-3, particularly long-chain, and omega-6 polyunsaturated fatty acids were significantly associated with lower blood pressure in adolescent boys, but not girls. Our results suggest that the relationships between dietary fatty acid intake and blood pressure in adolescents may be

moderated by gender.

Funders of the project:

NH&MRC Program Grant #353514

Heart Foundation/ Beyond Blue Strategic Research Initiative grant.

#### ANTENATAL AND PERINATAL DETERMINANTS OF BEHAVIOUR IN CHILDHOOD AND ADOLESCENCE: THE WESTERN AUSTRALIAN PREGNANCY COHORT (RAINE) STUDY

Monique Robinson, Wendy Oddy, Neil McLean.

This work has been conducted for Monique Robinson's MPsych/PhD candidature, a joint project between the Telethon Institute for Child Health Research and the School of Psychology at The University of Western Australia. Using the Raine Study cohort, the project is an in-depth analysis of the early life origins of behavioural development, including the identification of antenatal maternal lifestyle risk factors for later child and adolescent behavioural problems. Studies within the project have examined the effect of maternal psychosocial stress during pregnancy, cigarette smoking, alcohol use and hypertensive diseases of pregnancy on later behavioural outcomes to adolescence. Five publications have resulted from the project to date.

Funders of the project: NHMRC Program Grant #353514.

#### BREAST FEEDING DURATION AND ACADEMIC ACHIEVEMENT

Wendy Oddy, Jianghong Li, Stephen Zubrick, Andrew Whitehouse, Eva Malacova.

This project investigated the effect of breastfeeding duration on numeracy and literacy in a subset of the Raine Cohort children at ten years of age who attended government school in WA, independent of parental socioeconomic and demographic characteristics and home stimulation. The

study further examined gender differences in the effect of breastfeeding on numeracy and literacy attainment.

Funders of the project: Curtin Research Fellowship (Jianghong Li)

#### BREASTFEEDING AND METABOLIC SYNDROME

Wendy Oddy, Therese O'Sullivan, Rae-Chi Huang, Trevor Mori, Gina Ambrosini, Nicholas deKlerk, Stephen Zubrick, 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 14 years as defined by three criteria 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 14 years using age-specific adolescent criteria from the International Diabetes Federation (IDF), the National Cholesterol Education Program Adult Treatment Panel III (ATP), and a population-derived "high-risk" metabolic cluster variable. We showed that metabolic syndrome prevalence was 4.0% according to both IDF and ATP criteria while 26% were classified into the high-risk metabolic cluster. Breastfeeding cessation prior to two months of age was associated with an increased prevalence of the metabolic syndrome at 14 years as defined by both IDF and ATP criteria (breastfed <math>\leq 2</math> months=7%; breastfed 2+ months=4%;  $p < 0.05$ ). In addition, breastfeeding cessation before two months was associated with high waist circumference as defined by IDF criteria at 14 years (OR: 1.79; 95% CI 1.39-2.31) and 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.

#### Social determinants of child health/social epidemiology

##### PARENTAL WORK HOURS AND QUALITY OF DIET IN ADOLESCENTS

Jianghong Li, Wendy Oddy, Therese O'Sullivan, Gina Ambrosini.

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.

##### 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, 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, Anke van Eekelen, Monique Robinson, Jonathan Foster.

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

## 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.

## HOUSING AND CHILDREN'S HEALTH AND DEVELOPMENT

Dockery M, Kendall G, Li J, Strazdins L, Chan F, Ong R, Seymour R, Mahendran A

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:

Projects undertaken by Dockery M, Kendall G, Li J, Strazdins L, Chan F, Ong R, Seymour R, Mahendran and supported by Australian Housing and Urban Research Institute

## 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.

## CHILDHOOD DETERMINANTS OF RISKY SEXUAL BEHAVIOUR IN ADOLESCENCE: A PROSPECTIVE COHORT STUDY

Rachel Skinner, Martha Hickey, Eugen Mattes, Dorota Doherty, Anthony Smith, Susan Rosenthal, Spring Cooper, Michael Smith.

This research project aims to identify childhood factors which influence an adolescents' likelihood to initiate sexual activity at a young age, and engage in sexual risk taking. Risky sexual behavior contributes to unplanned teenage pregnancy, sexually transmitted infections (STIs) and adverse social, emotional and physical health outcomes in adolescence into adulthood. We have little understanding of early determinants of risky sexual behavior.

The Raine Study provided extensive biological, psychological, psychosocial, family, individual and environmental characteristics collected at all ages. This unique dataset is currently being utilised to undertake a world first analysis of causal pathways through early life to sexual risk-taking in adolescence.

Initial analyses show higher scores for Total Behavior Problems and the Externalizing Behavior subscale of the Child Behavior Checklist (CBCL) in participants who had already engaged in sexual intercourse compared to those who did not. In addition, participants who were identified with clinically recognized delinquent and aggressive behavioral problems at ages 5, 8, 10 and 13, were more likely to have engaged in sexual intercourse. These unique data indicating early predictors of risky sexual behavior in adolescence may help determine how and at what ages interventions may be effective.

Funders of the project: NH&MRC 634509.

## 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 projects aims to develop, test and disseminate a new intervention for childhood obesity. The approach is novel in that mothers will be the primary agents of change. There are several compelling reasons for this. Mothers play a critical role in shaping children's eating behaviours, and influence food choice through role modelling. It is likely that changes in the mother's eating and exercise habits will lead to a parallel change in the pre-pubertal child's eating and exercise behaviours.

Assessment protocols have been developed for the trial of the intervention program. These assessment protocols include self-report questionnaires and semi-structured interviews which will be administered to mothers and children both prior to commencing the intervention program and at completion of the intervention program.

The intervention program is based on a cognitive behavioural treatment (CBT) for obesity developed at the University of Oxford. The existing CBT has been now been modified for use with mothers of primary school children. Also, for the purposes of this project, modules focusing on parenting skills, educating parents about eating and exercise behaviours in children and promoting psychosocial wellbeing in children have been added to the original CBT.

At this stage it is anticipated that both a community and clinical trial of the intervention program will commence in 2011.

Funders of the project: Western Australian Health Promotion Foundation (Healthway).

### DEVELOPING EVIDENCE-BASED RECOMMENDATIONS FOR MANAGING CHILDHOOD OBESITY

Susan Byrne, Elizabeth Davis, Elizabeth Geelhoed, Eve Blair, Stephen Zubrick.

This study aims to identify the factors that contribute to the

development and persistence of overweight and obesity in children, as well as the factors that lead from overweight and obesity to the development of medical and psychosocial complications. Through the identification of such factors as well as a cost-analysis of the burden of overweight and obesity in children and a focus on the community aspects of childhood obesity we will be able to develop targeted, cost-effective and acceptable prevention and intervention strategies. Ultimately, this will allow effective strategies to be chosen for a particular set of circumstances, rather than applying blanket prevention and intervention strategies that may not be successful and would use unnecessary resources.

The study currently consists of 1645 children who were weighed and measured at school, of which 473 are taking part in the medical/psychosocial assessment stage of the study. In addition to the children from the community there are currently 59 children recruited into the study from the Obesity Clinic at PMH. Of the total sample of children, there are 101 classified as obese, 142 classified as overweight and 282 classified as healthy weight.

Findings from the GAD Study have shown an increasing tendency to pathology with increasing degree of adiposity on a comprehensive range of psychological and biomedical measures in primary school aged children. More specifically, we found that child BMI was significantly associated with higher levels of depression, increased body dissatisfaction, poor quality of life, lower self-esteem, greater eating disorder symptomatology, poor peer relationships and behavioural problems. An important conclusion from these findings is that even in young primary school-aged children the psychosocial burden of excess weight is significant and broad-reaching. Moreover, psychologically affected overweight children are likely to experience multiple clinically significant psychosocial problems.

Funders of the project: Western Australian Health Promotion Foundation (Healthway).

## Staff and Students 2010

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Kylie Blurton

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Laura Bond, MPH, BHSc

Nancy-Lee Boulton

Jenny Bourke, BE, MPH

Hollie Bowker, OCCTher

Nina Boydell, BA, Dip Ed

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Somer Dawson, BEcons, BHlth Sci(Hons)

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Assoc. Prof. Deborah Lehmann, MBBS, MSc  
Dr Jianghong Li, BA, MSc, PhD  
Assoc. Clin. Prof. Helen Leonard, MBChB, MPH  
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Kate Miller, BSc, MSc(Health Promotion)  
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Virginia Muniandy, BE(Early Childhood)  
Rose Murray, Diploma of Teaching (Primary),CAE  
Dr Raewyn Mutch, MBChB, DipRACOG, FRACP, PhD  
Dr Natasha Nassar, BEc, MPH, PhD  
Dr Nusrat Naseem MBBS, MPH  
Cathrine Nemer  
Hoan Nguyen, BAppSc  
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Dr Monique Robinson, BA(Hons)Psych, PhD  
Elke Scheepers, BA, AdvCert Tvl Cons  
Dr Claire Scrine-Bradfield, BA(Hons), PhD  
Carrington Shepherd, BA (Econs)  
Dr Adeleh Shirangi, PhD  
Dr Rachel Skoss, PhD  
Kylie Small  
Carolyn Smargiassi  
Grant Smith, BPsych, M Psych  
Dr Michael Smith, BA(Hons)(Psych), PhD  
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Kristy Staples, BA, Post Grad Dip Counsellor  
Fred Stacey, BA  
Kerry Stedman, BSc  
Michael Strack  
Alison Stubbs  
Wenxing Sun, BHSc  
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Karen Ugle B.Psych, AMAPS  
Anna Urbanowicz,BSc(OT)(Hons)  
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Assoc. Prof. Roz Walker, PhD, BA (Hons) Politics and Philosophy  
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Maude Walsh  
Alicia Watkins, BPsych, PGradDip(Psych)  
Linda Watson  
Felicity Watt, B.Psych, MSc  
Bethany Wayne  
Meredith West  
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Lydia Sung, PhD candidate, UWA  
Lauren Taylor, PhD candidate, UWA  
Svein Van-Oyen, PhD candidate, UWA  
Ellen Walker, Hons candidate, Curtin  
Sian Williams, PhD candidate, UWA  
Janice Wong, PhD candidate, UWA  
Susan Woolley, Hons candidate, Curtin  
Paula Wyndow, BSc Postgraduate Diploma, PhD candidate, Curtin

## Theses passed

Jessica Coles, BSc (Occupational Therapy) (Hons): Edith Cowan University: The Work Practices and Employment Patterns of parents of a child with Rett syndrome.

Dr Rae Chi Huang, MB BS, PhD, FRACP (paeds), DCH Cheers Raech : University of Western Australia: Childhood precursors of adult cardiovascular disease.

Emma Jaquet, M Clin Psych: University of Western Australia: The relationship between prenatal head size growth and behavioural development.

Olivia Knight, BSc (Occupational Therapy) (Hons): Edith Cowan University: Pubertal trajectory and the management of menstruation in females with Rett syndrome and Down syndrome.

Faye Lim, BMedSci (Hons). University of Western Australia: Experiences of Rett syndrome in China.

Janice Lim, (Hons). University of Western Australia:

Experience of Rett Syndrome in China.

Eva Malacova, PhD: University of Western Australia. PhD: University of Western Australia: Developmental pathways to childhood literacy and numeracy: the role of early health.

Divia Pillay, BSc (Occupational Therapy) (Hons): Edith Cowan University: Spirituality and Organised religion in supporting parents of children with Down syndrome and intellectual disability: A narrative review.

Nevada Pingault, BSc(MedSci)(Hons1), MASM, MAIMS, PhD: University of Western Australia: Epidemiology of Moraxella catarrhalis in the Upper Airway of Indigenous and Non Indigenous children in the Kalgoorlie community.

Kate Povee, BSc (Psychology) (Hons): Curtin University: Family functioning in families with a child with Down syndrome: A mixed methods approach.

Monique Robinson, PhD: University of Western Australia: Antenatal and perinatal determinants of behavior in childhood and adolescence: The Western Australian Pregnancy Cohort (Raine) Study.

Georgina Trotter, MBBS, (Hons). Notre Dame: Factors which increase parental concern about their child's weight.

Ellen Walker, BSocialWork (Hons): Curtin University: The experience of carers as their daughter with Rett syndrome transitions from late adolescence to adulthood.

Susan Woolley, (Hons): Curtin University: Dietary intake and food sources of fructose in adolescents.

## Awards

Helen Bailey, Student presentation prize Australasian Epidemiological Association Annual Scientific Meeting, September, 2010.

Lyn Colvin, Australian Postgraduate Award, 2006-.

Lyn Colvin, Stan and Jean Perron Award for Meritorious Performance, 2010.

Lyn Colvin, UWA Graduate Research Student Travel Award, 2010.

Aditya Deshpande, Colgate/International Association for Dental Research Travel Award, September 2010.

Stephanie Fehr, Friends of the Institute for Child Health Research Travel Award, September, 2010.

Kitty Foley, Friends of the Institute for Child Health Research Travel Award, September 2010.

Michele Hansen, Graduate Research Travel Award, The University of Western Australia, June 2010.

Deborah Lehmann, Hannah Moore, Kirsten Alpers, Consumer and Community Advisory

Council: Consumer and Community Participation Award, 2010.

Elizabeth Milne. Telethon Institute for Child Health Research, Leadership Award, 2010 – 12.

Hannah Moore, Perron Award 2010 for Meritorious Performance in PhD studies in 2009.

Hannah Moore, Australasian Epidemiological Association Student Award, 2010.

Hannah Moore, Telethon Institute for Child Health Research Postgraduate Student Forum First Prize, 2010.

Hannah Moore, Australasian Epidemiological Association Travel Award, 2010.

Hannah Moore, School of Paediatrics and Child Health – Travel Scholarship, 2010.

Hannah Moore, OMOZ Conference - Travel Scholarship, 2010.

Hannah Moore, Wenxing Sun, Deborah Lehmann, Travel support to attend the inaugural Australian Otitis Media Workshop, Darwin, 2010.

Wendy Oddy, NHMRC Achievement Award 2010-2011.

Wendy Oddy Career Development Fellowship 2011-2014.

Melissa O'Donnell, National Health and Medical Research Council Post-Doctoral Fellowship, 2010.

Melissa O'Donnell, ARC Discovery Grant: Public Health Approach to Child Abuse and Neglect: Antecedents, Outcomes and International Comparisons of Trends, 2010.

Colleen O'Leary, Australasian Epidemiological Association Travel Award.

Colleen O'Leary, NHMRC Post-doctoral Training Fellowship 2010-2013.

Therese O'Sullivan, Dietetics Association of Australia, Emerging Researcher Award, 2010.

Gavin Pereira, UWA Graduate Research Student Training Grant, 2010.

Kate Riddell, Lotterywest Travel Assistance Award, 2010.

Kate Riddell et al, Healthway grant for Evaluation of the Michael Leslie Pilbara Performing Arts Program, 2010.

Carrington Shepherd, a Stan and Jean Perron Top-Up Scholarship and Sidney Myer Health Scholarship (Sidney Myer Fund), 2009-2011.

Adeleh Shirangi, UWA Supplementary Travel Award, 2010.

Wenxing Sun, OMOZ Conference – Travel Scholarship, 2010.

Brilliana, von Katterfeld, the Western Australian State Government's Women's and Newborns' Health Network – Research Support, an Australian Postgraduate Award provided by The University of Western Australia and an Stan and Jean Perron Top-Up Scholarship.

Paula Wyndow, Curtin Postgraduate Scholarship, the Australian Federation of University Women (AFUW) – Research Support and a Stan and Jean Perron Award.

R. Huang. CIB on NHMRC Project Grant #1010495 : " The Effects of Omega-3 Fatty Acids on Novel Anti-Inflammatory Metabolites and Telomere Length in Early and Later Life: Potential Implications for Long-Term Cardiovascular Risk"

R. Huang. UWA Faculty of Medicine Postdoctoral Fellowship 2011-2012

## External Committees

### INTERNATIONAL

Eve Blair, Editorial Board of the Cochrane Review Group for Movement Disorders: member responsible for studies of cerebral palsy (1996-).

Sally Brinkman. International Consortium for the Monitoring of Child Development, (2010-).

Deborah Lehmann, Papua New Guinea Institute of Medical Research Buttressing Coalition, (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-).

Jianghong Li, Rural Sociology published by the American Rural Sociological Society, Associate Editor (June 2005-).

Elizabeth Milne, Childhood Leukemia International Consortium (2005-), Chair (2010-).

Wendy Oddy, Executive Committee Member, International Society for Research into Human Milk and Lactation, (2008-2010).

Wendy Oddy, International Advisory Council for the World Alliance of Breastfeeding Action, (2011-2013).

Melissa O'Donnell, International Child Maltreatment Data Management working group, (2009-).

Therese O'Sullivan, Dietitians Association of Australia: International Nutrition and Dietetics Terminology Working Group, (2010-ongoing).

Adeleh Shirangi, Fellow of ICOH Scientific Committee on Woman Health and Work, (2009-).

Adeleh Shirangi, Fellow of ICOH Scientific Committee on Reproductive Hazards in the Workplace, (2009-).

Adeleh Shirangi, International Commission on Occupational Health-ICOH, (2006-).

Catherine Taylor, Member of the Executive Board of the International Journal of Speech-Language Pathology.

Stephen Zubrick, Member, International Peer Review Committee for Team Grant: Vision, Hearing and Communications Disorders, Canadian Institutes for Health Research (2009-2010).

Stephen Zubrick, Editorial Board, Journal of Family Studies (previously the Australian Journal of Marriage and Family), 2005-).

### NATIONAL

Eve Blair, National committee for Australasian Academy of Cerebral Palsy and Developmental Medicine, (2006-).

Eve Blair, Australian Cerebral Palsy Register, policy

group,(2008-).

Eve Blair, Conference (2012) organizing committee for the Australasian Academy of Cerebral Palsy and Developmental Medicine. (2010-).

Carol Bower, Australian Birth Defects Society Committee member, (1999-).

Carol Bower, Australian Paediatric Surveillance Unit Scientific Review Panel, (1998-).

Carol Bower, Australian Paediatric Surveillance Unit Board member 1998-, Chair, (2003-).

Carol Bower, National Child Health Information Advisory Committee (AIHW), (1998-).

Carol Bower, National Perinatal Statistics Unit (AIHW) – Australian Congenital Anomalies Monitoring System Advisory Committee, (2007-).

Carol Bower, National Perinatal Statistics Unit (AIHW) – Expert Review Group; Assessing FASD data collection in Australia,(2009-).

Carol Bower, Food Standards Australia New Zealand, Folate Fortification Scientific Advisory Group, (2006-).

Sally Brinkman, National AEDI Strategic Policy Committee, (2008-).

Sally Brinkman, National AEDI Steering Committee, (2008-).

Sue Byrne, The Australian child and Adolescent Obesity Research Network (ACAORN) and co-chair ACAORN Longitudinal Studies Special Interest Group.

Nick de Klerk, Expert Reference Group, Australian Twin Registry, (2007-).

Nick de Klerk, Australian NHMRC Asbestos Working Party, (2003-).

Nick de Klerk, Australian Working Group developing Radiation

Protection Standard for Exposure to ELF, (2003-2010).

Nick de Klerk, Western Australian Medical Radiation and Cancer Working Party, (2004-).

Rae-Chi Huang. Australia New Zealand Obesity Society (ANZOS) Sydney October 2010

Tanyana Jackiewicz, National Child and Community Health Council, (2009-).

David Lawrence. Australian Early Development Index Data Linkage Steering Group, (2010-).

Deborah Lehmann, Member of the Australia21 Global Action Plan for the Prevention and Control of Pneumonia Steering group, (2008-).

Deborah Lehmann, Member of the Office of Aboriginal and Torres Strait Islander Health Services Otitis Media Technical Advisory Group, (2009-2010).

Deborah Lehmann, Member of the GSK Synflorix Advisory Panel,(2008-).

Deborah Lehmann, Member of data safety monitoring board for study of maternal pneumococcal immunization in the Northern Territory, ("PneuMum") (2005-).

Anne McKenzie, Consumers Health Forum of Australia, Senior Consumer Representative, (2004-)

Anne McKenzie, NPS RADAR Editorial Group, Consumer Representative, (2007-).

Anne McKenzie, NPS Consumer New Medicines Editorial Group Subcommittee, Chairperson,( 2007-).

Anne McKenzie ,Medicines Australia Code of Conduct Committee, Consumer Representative, (2006-).

Anne McKenzie , NHMRC Harmonisation of Research Ethics Review Committee, Consumer Representative,(2008-).

Anne McKenzie ,Consumer Representative, Population Health

Research Network Privacy, Ethics and Consumer Participation Committee, Consumer Representative,(2009-).

Anne McKenzie, Consumers Health Forum Program Reference Group, Consumer Representative. 2009-2010.

Wendy Oddy, Breastfeeding indicators for the National Breastfeeding Campaign, (2011-2015).

Therese O'Sullivan, Dietitians Association of Australia: International Nutrition and Dietetics Terminology Working Group.

Adeleh Shirangi, 2011 AEA National Conference, Organising Committee Member-Treasurer, (2010-current).

Catherine Taylor, Councillor, Australian Research Alliance for Children and Youth (ARACY).

Catherine Taylor, Mentor, New Investigators Network, Australian Research Alliance for Children and Youth (ARACY).

Roz Walker, Member, Australian Research Alliance for Children and Youth, (2008-).

Roz Walker, Member, Leaders in Indigenous Medical Education, (2008-).

Andrew Whitehouse, Asia Pacific Autism Conference: Scientific Committee.

Stephen Zubrick, Member, Australian Longitudinal Surveys Advisory Group (LSAG) (2007-).

Stephen Zubrick, Chair, Consortium Advisory Group, Longitudinal Study of Australian Children (2002-).

Stephen Zubrick, Member, VicHealth Indigenous Advisory Committee (2008-).

#### LOCAL

Eve Blair, Scientific advisory sub-committee to the Princess Margaret Hospital for Children Ethics Committee,(2007-).

Jenny Bourke, Committee member, Board of Management , Parents of Children with Disabilities (Inc).

Carol Bower, WA Perinatal and Infant Mortality Committee Member, (1993-).

Carol Bower, Prenatal Diagnosis Committee, Department of Health WA, (2001-).

Sally Brinkman, WA AEDI Coordinating Committee, (2008-).

Sally Brinkman, SA AEDI Coordinating Committee, (2008-).

Sue Byrne, member of the Australian Child and Adolescent Obesity Research Network (ACAORN) and the co-chair of the ACAORN Longitudinal Studies Special Interest Group.

Sue Byrne, Eating Disorder Research Society.

Sue Byrne, Healthway Health Research Sub-Committee.

Sue Byrne, UWA Vice Chancellor's Postdoctoral Fellowship Committee.

Nick de Klerk, Clinical Drug Trial Committee, Sir Charles Gairdner Hospital, 1986-88, (1990-).

Nick de Klerk, Mesothelioma Committee of Western Australia - co-ordinating the Western Australian Mesothelioma Register, (1989-).

Nick de Klerk, Busselton Population Medical Research Foundation, Board, (1997-).

Nick de Klerk, Busselton Population Medical Research Foundation, Scientific Committee, (1998-).

Nick de Klerk, Western Australian Medical Radiation and Cancer Working Party, (2004-).

Jenny Downs. Human,Research Ethics Committee, Princess Margaret Hospital for Children.

Rae-Chi Huang. Raine Management Committee

Tanyana Jackiewicz, Executive Advisory Group, Child and Youth

Health Network.

David Lawrence, HealthRight Reference Group, (2010-).

David Lawrence, Healthway Research Committee (2010-).

Deborah Lehmann, Vaccine Impact Surveillance Network Committee, WA, (1998 -).

Deborah Lehmann, Meningitis Centre Committee, (1998-).

Deborah Lehmann, Perinatal and Infant Mortality Committee, Ministry for Health, WA, (2005-).

Helen Leonard, Women's and Newborns' Health Network Executive Advisory Group.

Helen Leonard, Executive Committee Perth Epidemiology Group, (2008-).

Jianghong Li, The Raine Study Mental Health Committee.

Anne McKenzie, Health Consumers' Council WA, Chairperson, (2009-).

Anne McKenzie, WA Department of Health State health Executive Forum ICT Principle Committee, (2010-).

Anne McKenzie, WA Department of Health eHealth Community Reference Group, Chairperson (2009-).

Anne McKenzie, WA Department of Health Clinical Senate and Senate Executive Committee. (2009-).

Anne McKenzie, WA Department of Health WA Birth Defect Registry Advisory Group and Community Reference Group Chairperson (2007-).

Anne McKenzie, Silver Chain Human Research Ethics Committee, Lay Female Member.

Anne McKenzie, Royal Australasian College of Surgeons WA Audit of Surgical Mortality Committee, (2005-). 2010.

Anne McKenzie, WA Department of Health ehealth Program Delivery Committee, (2009-2010).

Anne McKenzie, Royal Perth Hospital Intensive Care Research Alliance, (2006- 2010).

Elizabeth Milne, Cancer Council WA Research Grants Committee, (2004-).

Hannah Moore, Australasian Epidemiological Association 2011 Conference Organising Committee, (2010-).

Hannah Moore, The Meningitis Centre Management Committee, (2008-).

Wendy Oddy, Ngala WA Professional Development Advisory Group, (2008-2011).

Wendy Oddy, Infant and Early Child Nutrition Working Group, (2007-2011).

Therese O'Sullivan, Dietitians Association of Australia: WA executive committee, 2009-ongoing).

Rose Murray, COAG Aboriginal Child Health Project Steering Group (2010-).

Rose Murray, Child and Adolescent Health Service's, Aboriginal Health Action and Advisory Committee (2010).

Adeleh Shirangi, AEA-Perth Epidemiology Group (PEG), Committee member, (2009-).

Grant Smith, Challis Evaluation Advisory Group.

Roz Walker, Member, WA Australian Early Development Index Committee, (2010).

Roz Walker, Member, Pilbara Child and Youth Project, (2009).

Roz Walker, Member, Pilbara Early Learning Alliance, (2008).

Roz Walker. Member, Student Reference Group, Telethon Institute for Child Health Research, (2008-).

Roz Walker, Childcare Links Advisory Group, South Hedland. (2008-).

Roz Walker, Member, Hedland Youth Stakeholder Action

Group. Executive Committee, South Hedland. (2007 -).

Roz Walker, Member, Aboriginal Collaboration Council for Applied Research and Evaluation. Telethon Institute for Child Health Research, (2008-).

## Presentations

### INTERNATIONAL

Karina Allen, Byrne, S. M., Stanley, F., & Crosby, R. The prevalence and course of eating disorders in a population-based sample of male and female adolescents: Results from the Western Australian Pregnancy Cohort (Raine) Study. Paper delivered at the 2010 International Conference on Eating Disorders, Salzburg, Austria, 2010.

Karina Allen, Fursland, A., Byrne, S. M., & Nathan, P. Enhanced cognitive behavior therapy (CBT-E) with and without preceding motivation-focused therapy. Poster presented at the 2010 International Conference on Eating Disorders, Salzburg, Austria, 2010.

Karina Allen, (Fursland, A., Byrne, S.M., & Allen, K. L.). Transdiagnostic CBT-E: A naturalistic trial comparing treatment completers with drop outs. Paper delivered at the 2010 International Conference on Eating Disorders, Salzburg, Austria, 2010.

Eve Blair, First report of the Australian Cerebral Palsy Register. AusACPDM meeting, Christchurch, March 2010.

Eve Blair, First report of the Australian Cerebral Palsy Register. AACPD meeting, Washington US, September 2010.

Ami Bebbington, Leonard H, Jacoby P, Christodoulou J, Ben-Zeev B, Bahi-Buisson N, Pineda M, Anderson A, Ravine D, Ho G, Smeets E, Percy A. The phenotype of deletions in MECP2: What do we know? 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Ami Bebbington (Freilinger M, Bebbington A, Lanator I, de Klerk N, Dunkler D, Seidl R, Leonard H, Ronen GM). Survival with Rett syndrome: 50 years on, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Sally Brinkman, Beatty A. The Developmental Status of Children in Indonesia: undertaking impact evaluations in developing countries. Invited Presentation. UNICEF Head Office, New York, June 2010.

Sally Brinkman, Monitoring Early Childhood in Developing Countries. Invited Keynote Presentation. Equity from the Start: 10 Years of the EDI and Beyond International Conference. Hamilton, Canada, June 2010.

Sally Brinkman, EDI in Australia. Invited Keynote Presentation. Equity from the Start: 10 Years of the EDI and Beyond International Conference. Hamilton, Canada, June 2010.

Sally Brinkman, The Developmental Status of Children in Indonesia compared to the World. Baseline results from the Early Childhood Education and Development Program in Indonesia. Invited presentation by the World Bank delivered to the President and Staff of the National Ministry of Policy and Planning. Jakarta, Indonesia, February 2010.

Daniel Christensen, (Sanson A, Christensen Daniel, Mitrou Francis, Lawrence David, Zubrick Stephen R). The role of temperament and parenting style as predictors of child emotional and behavioural problems. The International Society for the Study of Behavioural Development 21st Biennial International Congress, Lusaka, Zambia, July 2010.

Lyn Colvin, Birth defects, preterm birth and intrauterine growth in the offspring of women prescribed citalopram during pregnancy, (oral presentation, Platform Session) a joint annual meeting: 23rd International Conference for the Organization of Teratology Information Specialists; and the 50th Annual Meeting of the Teratology Society, 'Healthy Lifestyles for Parents and Children,' Louisville, Kentucky, USA, June 2010.

Lyn Colvin, The safety of citalopram exposure during pregnancy - maternal characteristics, birth outcomes and early hospital admissions for 1157 children, (poster presentation). 26th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Brighton, UK, August 2010.

Lyn Colvin, Data linkage and pharmacovigilance in pregnancy in WA, (oral presentation) Centre for Paediatric Epidemiology and Biostatistics University College London - Institute of Child Health, London, UK, August 2010.

Nick deKlerk, Risk assessment of carcinogenetic hazards in mesothelioma (and Session Chair). 5th Asia Pacific Organization for Cancer Prevention Conference, Istanbul, 2010.

Nick deKlerk, Future burden of malignant mesothelioma in Western Australia. International Mesothelioma Interest Group Conference, Kyoto, 2010.

Nick deKlerk, Some non-technical aspects of data integration – consumer and community support and engagement. Bridging the gap in biomedical genetics. Wellcome Trust Scientific Conference, Cambridge, 2010.

Nick deKlerk, (Paper), Using cross agency linked data: an overview and some findings from the Developmental Pathways Project, Manitoba Centre for Health Policy 20th Anniversary Conference, 2010.

Nick deKlerk, (Paper), Birthweight, zygosity, sex, and gestation in Western Australian twins, 13th International Congress on Twin Studies, Seoul, 2010.

Nick deKlerk, (Paper), Familial associations for malignant mesothelioma after exposure to blue asbestos. Australian Lung Cancer Conference, Melbourne, 2010.

Aditya Deshpande, Leonard H, Bebbington A, Slack-Smith L. Investigating dental service use: Children with intellectual disability in Australia, 88th General Session International

Association for Dental Research, Barcelona (poster), July 2010.

Jenny Downs, Carter P, Anderson A, Palmer G, Roye D, van Bosse H, Bebbington A, Larsson E-L, Smith B, Baikie G, Torode I, Ellaway C, Bergman A, Fyfe S, Leonard H. Clinical guidelines for the management of scoliosis in Rett syndrome patients, 11th Annual Rett Syndrome Symposium, Leesburg, Virginia (poster), June 2010.

Jenny Downs, Bebbington A, Jacoby P, Leonard H. (invited) Gross motor and hand skills in Rett syndrome, Diagnosis, Genetics, Epidemiology and Clinical Management, Peking University First Obstetrics and Paediatrics Hospital, Beijing, January 2010.

Jenny Downs, Bebbington A, Kaufmann WE, Leonard H. Longitudinal hand function in Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh, October 2010.

Jenny Downs, Leonard H, Hill K. Measuring steps with the StepWatch™ Activity Monitor in Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Jenny Downs, Geranton S, Bebbington A, Jacoby P, Bahi-Buisson N, Ravine D, Leonard H. Atypical responses to pain in Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Jenny Downs ( Miller DJ, Corona J, Downs J, Akbarnia B, Blakemore LC, Betz RR, Campbell RM, Johnston CE, McCarthy RE, Roye DP Jr, Skaggs DL, Smith JT, Snyder BD, Sponseller PD, Sturm PF, Thompson GH, Yazici M, Vitale MG, Flynn JM). To operate or not to operate? Determining the optimal timing of surgical intervention for patients with early onset neuromuscular scoliosis, 4th International Congress on Early Onset Scoliosis and the Growing Spine, Toronto, November 2010.

Jenny Downs (Corona J, Miller DJ, Downs J, Akbarnia B,

Blakemore LC, Betz RR, Campbell RM, Flynn JM, Johnston CE, McCarthy RE, Roye DP Jr, Skaggs DL, Smith JT, Snyder BD, Sponseller PD, Sturm PF, Thompson GH, Yazici M, Vitale MG). Finding the tipping point: When should surgery be performed in children with early onset idiopathic scoliosis? 4th International Congress on Early Onset Scoliosis and the Growing Spine, Toronto (eposter), November 2010.

Jenny Downs (M Lotan, Schenker R, Downs J, Wine J). Assessment of the conductive education (PETO) intervention for children with Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Pat Dudgeon, P., Tania Jones, Kerry Kelly, K, Roz Walker, & Clinton Schultz, Invited symposium Cultural Competence: Working with Australian Aboriginal and Torres Strait Islander People, 27th International Congress of Applied Psychology (ICAP), Melbourne, July 2010.

Pat Dudgeon, P., Tania Jones, Vicki Hovane, & Roz Walker, Symposium: The lives of contemporary Australian Aboriginal Women, 27th International Congress of Applied Psychology, Melbourne, July 2010.

Stephanie Fehr, Bebbington A, Ellaway C, Rowe P, Leonard H, Downs J. Altered attainment of milestones is associated with earlier diagnosis of Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh, October 2010.

Stephanie Fehr, Downs J, Bebbington A, Leonard H. Atypical presentations and specific genotypes are associated with a delay in diagnosis, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Stephanie Fehr, Bebbington A, Nassar N, Downs J, de Klerk N, Leonard H. Changes in incidence and prevalence of Rett syndrome in Australia, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Stephanie Fehr, Downs J, Bebbington A, Leonard H. Atypical presentations and specific genotypes are associated with a

delay in diagnosis, 11th Annual Rett Syndrome Symposium, Virginia, Leesburg, (poster), June 2010.

Stephanie Fehr (Zhang J, Bao X, Cao G, Jiang S, Zhu X, Lu H, Jia L, Pan H, Fehr S, Leonard H, Ravine D, Wu X), What does the nature of the MECP2 mutation tell us about parental origin and recurrence risk in Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Kitty Foley, Bebbington A, Jacoby P, Girdler S, Leonard H, Downs J. Longitudinal video analysis of gross motor abilities of girls and women with Rett syndrome, 2nd European Conference on Rett Syndrome Edinburgh, October 2010.

Michele Hansen, Twins born following Assisted Reproductive Technology: perinatal outcome and admission to hospital, 13th International Conference on Twin Studies, Seoul, 2010.

Rae-Chi Huang. Novel lifecourse adiposity trajectories and the prediction of adolescent insulin resistance. ANZOS ASM Sydney 2010

Rae-Chi Huang. Hypothalamic pituitary adrenal axis genetic variation is associated with antenatal growth and postnatal blood pressure simultaneously. ANZOS ASM Sydney 2010

Tanyana Jackiewicz. Qualitative research in a health services focused research agenda 16th Annual Qualitative Health Research Conference, International Institute for Qualitative Health Methodology, Vancouver, Canada, October 2010.

Olivia Knight, Leonard H, Girdler S, Bourke J, Bebbington A, Sifarakas A. Pubertal trajectory in females with Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh (poster), October 2010.

Deborah Lehmann (Pomat W, Phuanukoonnon S, Van den Biggelaar A, Francis J, Orami T, Jacoby P, Holt P, Siba P, Lehmann D, Richmond P). Immunogenicity of neonatal and early infant pneumococcal conjugate vaccination and pneumococcal polysaccharide vaccine booster in Papua New

Guinea. International Neonatal and Maternal Immunization Symposium (INMIS 2010), Antalya Turkey, March 2010.

Deborah Lehmann (Van den Biggelaar A, Bosco A, Laing I, Pomat W, Phuanukoonnon S, Richmond P, Siba P, Lehmann D, Holt P). Immunophenotypic analysis of T-cell immunity to neonatal pneumococcal conjugate vaccination in high-risk Papua New Guinean infants. International Neonatal and Maternal Immunization Symposium (INMIS 2010), Antalya Turkey, March 2010.

Deborah Lehmann (Moberley S, Leach AJ, Mulholland EK, Morris P, Balloch A, Carapetis J, Tang M, Torzillo P, Andrews R, Lehmann D). Pneumococcal serotype specific antibody in Indigenous Australian women and infants enrolled in a maternal vaccination trial (PneuMum). International Neonatal and Maternal Immunization Symposium (INMIS 2010), Antalya Turkey, March 2010.

Deborah Lehmann (Pomat W, Phuanukoonnon S, Van den Biggelaar A, Francis J, Orami T, Jacoby P, Holt P, Siba P, Lehmann D, Richmond P, PNG Neonatal PCV Trial Team). Alternative pneumococcal vaccination schedules for high-risk populations: immunogenicity of neonatal pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine in PNG children. Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Deborah Lehmann (Van den Biggelaar A, Bosco A, Laing I, Pomat W, Phuanukoonnon S, Devitt C, Nadal-Sims M, Richmond P, Deborah Lehmann (Siba P, Lehmann D, Holt P)). Immunophenotypic analysis of T-cell immunity to neonatal pneumococcal conjugate vaccination in high-risk Papua New Guinean infants. Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Deborah Lehmann (Van den Biggelaar A, Francis J, Pomat W, Michael A, Nadal-Sims M, Devitt C, Phuanukoonnon S,

Richmond P, Siba P, Lehmann D, Holt P). Early Streptococcus pneumoniae and Haemophilus influenzae carriage impairs development of protective T helper 1 responses in Papua New Guinean infants. Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Deborah Lehmann (Aho C, Greenhill A, Phuanukoonnon S, Michael A, Moberley S, Pomat W, Siba P, Richmond P, Lehmann D, PNG Neonatal PCV Trial Team). Impact of neonatal and early infant pneumococcal conjugate vaccination on pneumococcal carriage and suppurative otitis media in Papua New Guinea. Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Deborah Lehmann, Jacoby P, Carville K, Bowman J, Riley T, Kalgoorlie OM Research Project Team. Predictors of carriage of Streptococcus pneumoniae amongst Australian Aboriginal and non-Aboriginal children. Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Deborah Lehmann (Bergmann A, Binks M, Hare K, Bowman J, Jones J, Riley TV, Leach AJ, Smith-Vaughan H, Lehmann D). Community-based surveillance of Streptococcus pneumoniae carriage as an early warning system to monitor pneumococcal disease in Western Australian Aboriginal communities. Deborah Lehmann, Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Helen Leonard, (invited) Diagnosis and epidemiology of Rett syndrome, Peking University First Obstetrics and Paediatrics Hospital, 9-11, Beijing, January 2010.

Helen Leonard, Downs J, Jian L, Bebbington A, Jacoby P, Nagarajan L, Ravine D, Woodhead H. A preliminary exploration of the possible non-epileptic effects of sodium valproate in Rett syndrome patients, 2nd European Conference on Rett

Syndrome, Edinburgh (poster), October 2010.

Helen Leonard, Downs J, Bebbington A, Fehr S. Development of a minimum Rett syndrome dataset, 2nd European Conference on Rett Syndrome, Edinburgh, October 2010.

Anne McKenzie INVOLVE (UK) Conference, Public Involvement in Research: Innovation and Impact. Invited plenary speaker. November 2010.

Anne McKenzie, Hangzhou Women's Hospital and Zhejiang Cancer Hospital, China, July 2010.

Hannah Moore, Using record linkage to investigate epidemiological perspectives of acute lower respiratory infections in Western Australian children, Centre for Evidence-Based Child Health, Institute for Child Health, University College London, United Kingdom, July 2010.

Hannah Moore, Lehmann D, De Klerk N, Jacoby P, Richmond P. Reduction in disparity in pneumonia hospitalisations between Aboriginal and non-Aboriginal children in Western Australia. Seventh International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 7), Tel Aviv Israel, March 2010.

Wendy Oddy, 2010 Medical Research Council UK, Cambridge University, Lunchtime series of talks' Nutritional factors associated with child mental health, May 2010.

Wendy Oddy, WABA Forum - (World Alliance for Breastfeeding Action) Enabling mothering: keeping mothers and babies together Penang, Malaysia. Keynote address: Societal benefits of breastfeeding, October 2010.

Wendy Oddy, The Power of Programming: International Conference on Developmental Origins of Health and Disease. Nutritional programming for later diabetes risk. Munich, Germany, May 2010.

Wendy Oddy, 9th Congress of the International Society for the Study of Fatty Acids & Lipids (ISSFAL), Munich, Germany oral presentation' Longitudinal associations between omega-3 fatty acids and depression in adolescence , May-June 2010.

Melissa O'Donnell, "Characteristics of Non-Aboriginal and Aboriginal children and families with substantiated child maltreatment: a population based study." International Congress on Child Abuse and Neglect, Hawaii, September 2010.

Melissa O'Donnell, Fluke, J. (first author) International Child Maltreatment Data Collection Programs: Context, Perspectives, and Prospects for Development" International Congress on Child Abuse and Neglect, Hawaii, September 2010.

Melissa O'Donnell, Lancet Article: International comparisons of trends in child abuse and neglect. International Congress on the Prevention of Child Abuse and Neglect, Hawaii, United States, September 2010.

Melissa O'Donnell, Record linked health and child protection data: Surveillance, monitoring, risk factors and outcomes, Institute of Child Health, University College London, September 2010.

Tracy Reibel, The evaluation of Innovative Health Services for Homeless Youth in Perth, Western Australia, International Conference on Youth Work and Youth Studies, 2010.

Tracy Reibel, Mind the Gap: conversations on youth work and youth studies that contribute to research, theory and practice on work with young people, Glasgow, Scotland, September 2010.

Adeleh Shirangi , Fritschi L, Holman CDJ. Stress, Anxiety and Depression in Female Veterinarians, RHICOH Taipei-Taiwan, April 2010.

Adeleh Shirangi , Fritschi L, Holman CDJ, Bower C. Birth Defects in Offspring of Female Veterinarians. EPICOH-MEDICHEM 2010, Taiwan, April 2010.

Sven Silburn, The Australian Early Development Index (AEDI) Indigenous Adaptation Study. Invited Keynote Presentation. Equity from the Start: 10 Years of the EDI and Beyond

International Conference. Hamilton, Canada, June 2010.

Katie Suriano, J Curran, SM Byrne, TW Jones, EA Davis, Fatness, fitness and increased cardiovascular risk in children, The Obesity Society Annual Scientific Meeting. San Diego CA, October 2010.

Anna Urbanowicz, Downs J, Bebbington J, Jacoby P, Girdler S, Leonard H. The use of equipment and respite services and caregiver health among Australian families living with Rett syndrome, 2nd European Conference on Rett Syndrome, Edinburgh (poster). October 2010.

Roz Walker and Christopher Sonn, Extending Cultural Competence through Critical Praxis: What does that really mean? Fourth International Conference of Psychology Education, University of New South Wales, Sydney, July 2010.

Roz Walker and Chris Sonn, Aboriginal and Torres Strait Islander Issues in Psychology: Professional Practice Issues, Fourth International Conference of Psychology Education, University of New South Wales, Sydney, July 2010.

Roz Walker, Cultural Competence: Working with Australian Aboriginal and Torres Strait Islander People, 27th International Congress of Applied Psychology, Melbourne, July 2010.

Roz Walker, Aboriginal and Torres Strait Islander Health Policy Context 27th International Congress of Applied Psychology, Melbourne, July 2010.

## NATIONAL

Karina Allen, (Fursland, A., Allen, K. L., Watson, H., & Byrne, S.M.). Eating disorders – not just an adolescent issue? Paper presented at the 8th Annual Conference of the Australian and New Zealand Academy of Eating Disorders, Auckland, New Zealand, 2010.

Karina Allen, (Watson, H., Fursland, A., Allen, K. L., Byrne, S. M., & Nathan, P.). Enhanced cognitive behaviour therapy

(CBT-E) for eating disorders: Does early response affect outcomes? Paper presented at the 8th Annual Conference of the Australian and New Zealand Academy of Eating Disorders, Auckland, New Zealand, 2010.

Jenny Bourke, Leonard H, Bower C. IDEA database: Trends in prevalence of intellectual disability in WA, 45th Annual Conference Australasian Society for Intellectual Disability, Brisbane, September-October 2010.

Eve Blair, Cerebral Palsy: why have rates not changed? Research update for donors to the Cerebral Palsy Foundation, Sydney, March 2010.

Sally Brinkman, Unit Record Files – How to make the most effective use of a jurisdiction's unit record file. AEDI Policy Forum, Aust. Govt. Melbourne, November 2010.

Sally Brinkman, Predictive Validity of the AEDI. AEDI Policy Forum, Aust. Govt. Melbourne, November, 2010.

Sally Brinkman, AEDI Results for South Australia. Invited presentation. Mission Australia, Adelaide. September, 2010.

Sally Brinkman, Goldfeld S., Sayers M. Symposia. The Status of Child Development in Australia. Australian Institute, 2010.

Sally Brinkman, The Developmental Status of Children in Indonesia: undertaking impact evaluations in developing countries. Invited Presentation. AusAid Head Office with Papua New Guinea and Indonesia via videoconference. Canberra, Australia, October 2010.

Sally Brinkman, Symposia. The Status of Child Development in Australia. Australian Institute of Family Studies (AIFS) Conference. Melbourne, Australia, July 2010.

Sally Brinkman, National Status of Child Development in Australia. Invited Keynote. World Education Forum. Adelaide. Australia, March 2010.

Sally Brinkman, The Australian Early Development Index – implications for the Non-Government Sector in South

Australia. Invited Keynote by the Department of Education and Children's Services. Adelaide. March 2010.

Sally Brinkman, (Goldfeld S., Brinkman S.). AEDI: Understanding the detail and setting the scene. Plenary Session. AEDI Policy Forum, Aust. Govt. Melbourne, November 2010.

Lyn Colvin, "Pharmacovigilance in pregnancy using linked data," (workshop presentation, 'Data Methods Workshop: Measuring the impact of medicines policy and practice on drug utilisation, costs and health') Lyn Colvin, National Medicines Symposium 2010, 'Medicines in People's Lives' Melbourne, Australia, May 2010.

Lyn Colvin, "The safety of citalopram exposure during pregnancy – a case study in pharmacovigilance using linked health datasets," (oral presentation) National Medicines Symposium 2010, 'Medicines in People's Lives' Melbourne, Australia, May 2010.

Lyn Colvin, "Pharmacovigilance in pregnancy: a case study of citalopram exposure during pregnancy – maternal characteristics, birth outcomes and early hospital admissions for 1157 children," (oral presentation) Australian Epidemiological Association, Sydney, Australia, September 2010.

Nick deKlerk, Trends in the incidence of malignant mesothelioma in Western Australia. 7th Perth Mesothelioma Group Symposium, Perth, 2010.

Aditya Deshpande, Leonard H, Bebbington A, Slack-Smith L. Dental health and services: Children with intellectual disability in Australia, International Association for Dental Research (Australian/New Zealand Division Golden Jubilee Meeting), Kiama (poster), September 2010.

David Lawrence, Confidentiality in practice: A user perspective. Australian Government Statistical Forum, Canberra, 2010.

Deborah Lehmann, Willis J, Moore H, Giele C, Murphy D, Keil AD, Harrison C, Bayley K, Watson M, Richmond P. Impact of pneumococcal conjugate vaccine on invasive pneumococcal disease incidence in Western Australia: declines in children and non-Aboriginal adults but increase in Aboriginal adults. The Australasian Society for Infectious Diseases Annual Scientific Meeting; Darwin NT, May 2010.

Deborah Lehmann (Pomat W, Lehmann D, Phuanukoonnon S, Van den Biggelaar A, Francis J, Orami T, Jacoby P, Holt P, Siba P, Richmond P). Sustained immune responses to neonatal and early infant pneumococcal conjugate vaccination followed by pneumococcal polysaccharide vaccine booster in Papua New Guinea. The Australasian Society for Infectious Diseases Annual Scientific Meeting; Darwin NT, May 2010.

Helen Leonard, Keynote: Using epidemiology to understand the determinants of intellectual disability disorders and their outcomes for affected children and their families, 45th Annual Conference Australasian Society for Intellectual Disability, Brisbane, September- October 2010.

Anne McKenzie, Consumers Health Forum of Australia, December 2010: Medicines Packaging and Labelling Workshop, invited speaker, December 2010

Anne McKenzie, Medicines Australia Conference, Stepping Out -Stepping up, invited plenary speaker, October 2010

Anne McKenzie, NPS Community Advisory Group, Meeting Sydney, invited speaker. August 2010

Anne McKenzie, Primary Healthcare Research Conference, Darwin, July 2010.

Anne McKenzie, National Medicine Symposium, Melbourne, invited plenary speaker, May 2010.

Elizabeth Milne, Fetal growth, folate and childhood cancer. CSIRO Nutritional Genomics Symposium, Adelaide, July 2010

Elizabeth Milne, Perspectives in Child Health talk. Nutrition and DNA Health, TICHR, September 2010.

Elizabeth Milne, Greenop K, de Klerk NH, van Bockxmeer F, Bailey HD, Miller M, Norris MD, Haber M, Scott RJ, Bower C, Attia J, Armstrong BK, on behalf of the Aus-ALL Consortium, 2010.

Elizabeth Milne, Aus-ALL: Folate metabolising genes, folate supplementation and risk of childhood ALL. Australian and New Zealand Children's Haematology/Oncology Group Annual Scientific Meeting, Sydney, September 2010.

Hannah Moore, Interactions between respiratory viruses and otitis media bacterial pathogens in asymptomatic children: Implications for interventions targeting specific pathogens. Australian Otitis Media Workshop, Darwin, NT, May 2010.

Hannah Moore, Lehmann D, Richmond P, De Klerk N. Population attributable fractions of infant and maternal risk factors for respiratory infections in children: a population-based record linkage study. Australasian Epidemiological Association Annual Conference; Sydney, NSW, September 2010.

Hannah Moore, Lehmann D, Richmond P, de Klerk N. Using population-based data to investigate infant and maternal risk factors for hospitalisations for acute lower respiratory infections in children. Childhood and Adolescent Health Research Symposium, Subiaco, WA, October 2010.

Hannah Moore, Lehmann D, De Klerk N, Jacoby P, Richmond P. Reduction in pneumonia hospitalisations in Western Australian children and the likely contribution of pneumococcal vaccines. The Australasian Society for Infectious Diseases Annual Scientific Meeting; Darwin NT, May 2010.

Wendy Oddy, National Nutrition Society of Australia, Nutrition Update Day, May 2010.

Therese O'Sullivan, Nutrition Society of Australia National Conference, December 2010.

Therese O'Sullivan, Dietitians Association of Australia national

conference, May 2010.

Sven Silburn, The Australian Early Development Index (AEDI) Indigenous Adaptation Study. Invited Keynote Presentation. National Policy Forum, Melbourne, November 2010.

Sven Silburn, Data systems for the monitoring of implementation and outcomes. Invited paper at the Effective Integration of Services for Children and Families national symposium, Darwin, August 2010.

Sven Silburn and Jonathan Carapetis, Indigenous education – the need for evidence. Invited Keynote Presentation at the Menzies Foundation national symposium on Closing the Gap in Indigenous Education, Melbourne, July 2010.

Catherine Taylor. Late language emergence is a risk for Specific Language Impairment: Towards an understanding of developmental mechanisms. Research Seminar presented at the Murdoch Children's Research Institute, Melbourne, July, 2010.

Roz Walker, An evaluation of Cultural Competence Assessment Tools (trial version) to improve the effective delivery of health care to Aboriginal families Women's and Newborn Child Health Network, Perth Yacht Club, WA, 2010.

Roz Walker, The AEDI in action: Reflections the AEDI pilot projects in the Pilbara, Launch of The Western Australian Early Development Index Results, Como, WA, May 2010.

Roz Walker, Using the AEDI to Evaluate Programs to identify funding opportunities Australian Early Development Index (AEDI) AEDI Local Champions Training Forum, Como, WA, May 2010.

Stephen Zubrick, Panel Member. Children at Risk: What is working for Australia? Australian Government Social Inclusion Conference, Melbourne Convention Centre, Southbank, Victoria, January 2010.

Stephen Zubrick, (Invited Keynote) Where do strengths come from? The contribution of childhood in the course of human

development. 6th Australian Family and Community Strengths Conference, Newcastle, December 2010.

Stephen Zubrick, (Invited Workshop Facilitator) Integrating the Australian Early Development Indicator into Policy. National Policy Forum, Melbourne, November 2010.

Stephen Zubrick, (Invited Keynote) Implications of the human development paradigm for implementation and prevention science. Effective Integration of Services for Children and Family Symposium, Darwin, August 2010.

### LOCAL

Karina Allen, Treating eating disorders in the real world: An update from the Eating Disorders Programme at the Centre for Clinical Interventions. Presented at the Australian Association of Cognitive Behaviour Therapy (AACBT). Local Event for Western Australia, March 2010.

Eve Blair, P values and statistical significance. Research meeting of Dept of Paediatric Rehabilitation, PMH. October 2010.

Lyn Colvin, "Pharmacovigilance in pregnancy: a case study of citalopram exposure during pregnancy – maternal characteristics, birth outcomes and early hospital admissions for 1157 children," (oral presentation) Child and Adolescent Health Research Symposium, Princess Margaret Hospital, Perth, Australia, October 2010.

Lyn Colvin, "Data linkage and pharmacovigilance in pregnancy in WA," (oral presentation) Health Information Technology Forum, Perth, Australia, November 2010.

Gayle Corbould, Tanyana Jackiewicz and Shawn Phillips Who Cares: A Review of the Services Provided to Young People who Attend Emergency Departments with Deliberate Self Harm, Suicide Ideation, or a Suicide Attempt in the Perth Metropolitan Area. Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Jenny Downs, Bebbington A, Kaufmann WE, Leonard H. Longitudinal hand function in Rett syndrome, Childhood and Adolescent Health Research Symposium, Princess Margaret Hospital and Telethon Institute for Child Health Research, Perth, October 2010.

Jenny Downs, Understanding rare disorders: The example of Rett syndrome, Paediatric Physiotherapy Forum, Curtin University, Perth, February 2010.

Stephanie Fehr, Bebbington A, Ellaway C, Rowe P, Leonard H, Downs J, Altered attainment of milestones is associated with earlier diagnosis in Rett syndrome, Childhood and Adolescent Health Research Symposium, Princess Margaret Hospital and Telethon Institute for Child Health Research, Perth, October 2010.

Stephanie Fehr, Bebbington A, Nassar N, Downs J, Ronen GM, de Klerk N, Leonard H, Trends in the diagnosis of Rett syndrome in Australia: what do they teach us?, Childhood and Adolescent Health Research Symposium, Princess Margaret Hospital and Telethon Institute for Child Health Research, Perth, October 2010.

Stephanie Fehr, Downs J, Bebbington A, Leonard H, Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome, Childhood and Adolescent Health Research Symposium, Princess Margaret Hospital and Telethon Institute for Child Health Research, Perth, October 2010.

Rebecca Glauert, "Developmental Pathways in WA Children Project." Presentation. Start Stronger, Live Longer Symposium, Perth, WA, June 2010.

Tanyana Jackiewicz, Karen Forde, Sue Kiely, Rachel Skoss and Kim Clark Working with Providers and Policy Makers to facilitate evidence based change: the Child and Adolescent Community Health Project. Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Amanda Langridge, Social and racial inequalities in infant outcomes in Western Australia, 1984-2006. Start Stronger, Live Longer Symposium, Perth, WA, June 2010.

Amanda Langridge, Li, J., Nassar, N. & Stanley, F. "Social and racial inequalities in infant outcomes in Western Australia, 1984-2006" (Invited Presentation). Start Stronger, Live Longer Symposium, Perth, WA, June 2010.

David Lawrence, The use of record linkage research to inform service delivery policy: Improving educational outcomes for Aboriginal children and young people. Australian Government Leadership Network Conference, Perth, 2010.

Moore H. Infectious disease research and respiratory infections in children. Have a Go Day News (Community Group), Perth, WA, September 2010.

Moore H. Where should we focus prevention efforts for reducing hospitalisations for acute lower respiratory infections in Western Australian children? Telethon Institute for Child Health Research Division of Population Sciences Annual Scientific Meeting, Perth WA, April 2010.

Rose Murray, 'Start Stronger Live Longer Healthworker Resource Manual'. Child and Adolescent Community Health Statewide Aboriginal Health Worker Practice Development Workshop, Perth, November 2010.

Melissa O'Donnell, Child Abuse and Neglect: Surveillance, Monitoring and Risk factors. Department for Child Protection, Perth, WA, June 2010.

Melissa O'Donnell, Child Abuse and Neglect: Vulnerable children and families, Start Stronger, Live Longer Symposium, Perth, WA, June 2010.

Therese O'Sullivan, Fructose intake and food sources. Raine Study Scientific Meeting, Perth, Australia, October 2010.

Tracy Reibel, Tanyana Jackiewicz, and Michael Robinson. The Evaluation of Innovative Health Services for Homeless Youth in Perth, Western Australia: preliminary findings.

Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Sven Silburn, A Childhood Development Framework: Building pathways to resilience. Invited keynote presentation. Gladstone Communities for Children Professional Forum, Gladstone, May 2010.

Grant Smith, Janet Hornbuckle, Tanyana Jackiewicz, Rachel Skoss, Ric Fordham Calculating the burden of gestational diabetes: Short-term hospitalisation costs in Western Australia. Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Grant Smith, Tanyana Jackiewicz. Can hospital and emergency department records be used to identify children at risk of serious injury? Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Grant Smith, Trends in hospitalisations for asthma in Western Australia: Admissions, readmissions, and treatment from 2000 to 2007. Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Grant Smith and Tanyana Jackiewicz, Phase I: Evaluation of the First Phase of the evaluation of the evaluation of the Baby Friendly Hospital Initiative. Western Australian Women's and Newborns Research Symposium, November 2010.

Catherine Taylor, Late language emergence is a risk for Specific Language Impairment: Towards an understanding of developmental mechanisms. Seminar presented to the Child and Adolescent Health Service Speech Pathology Paediatric Special Interest Group, Perth, Western Australia, July 2010.

Brilliana von Katterfeld, Perinatal issues in CALD populations: The pregnancy and postpartum experiences of women from Aghanistan, Burma, China, Sudan and Vietnam. Western Australian Child and Youth Health Network Research Symposium PMH, October 2010.

Roz Walker, An evaluation of Cultural Competence

Assessment Tools (trial version) to improve effective delivery of health care to Aboriginal families. Western Australian Child and Youth Health Network Research Symposium. PMH, WA, October 2010.

Roz Walker, Stories of Loss, Women's and Newborn Health Network, Research Symposium, King Edward Memorial Hospital, Subiaco, WA, November 2010.

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Roz Walker, Improving communication and decision making with Aboriginal families WA Child and Youth Health Network Research Symposium MacDonald Lecture Theatre, Princess Margaret Hospital Subiaco, WA, November 2010.

Roz Walker, Ailsa Munns & Valma Banks, Yanan Ngurra-Ngu Walalja community Families Program –Halls Creek, Child and Adolescent Health Research Symposium, Princess Margaret Hospital, WA, October, 2010.

Roz Walker, Understanding White Privilege: Cultural competence and professional development, King Edward Memorial Hospital, Perth, July, 2010.

Roz Walker, Improving communication and decision making with Aboriginal families, Womens' and Newborn Health Network Subiaco, February 2010.

Ellen Walker, Love and war – emergent adults, carers, and society: The experience of carers as their daughter with Rett syndrome transitions from late adolescence to adulthood, Mark Liveris Health Sciences Research Student Seminar, Curtin University, 8 November, 2010, Perth.

Andrew Whitehouse, Searching for genes influencing language development. Raine Study Scientific Meeting, Perth, Australia, October 2010.

Andrew Whitehouse, Investigating neurodevelopmental disorders at different aetiological levels. Curtin University Psychology Departmental Seminar, Perth, Australia, October 2010.

Andrew Whitehouse, Six things I've learnt along the way. UWA Psychology Conference (Keynote), Perth, Australia, October 2010.

Stephen Zubrick, Catherine Taylor. Developmental mechanisms in late language emergence and Specific Language Impairment. School Psychologists' Association of Western Australia Annual Conference, Perth, Western Australia, September 2010.

## Overview

The Vaccine Trials Group (VTG) aims to improve the health of the community through immunization and the prevention of infectious disease.

VTG has been involved in a number of exciting projects studying new vaccines. One of these vaccines is for the prevention of staphylococcus aureus or "Golden Staph" infections that are increasingly difficult to treat as a result of antibiotic resistance. Respiratory Syncytial Virus (RSV) is the most common cause of serious viral infections chest infections or bronchiolitis in babies. VTG is studying a potential breakthrough is a vaccine that can be given as nasal drops. We have also started a study of a vaccine against dengue fever, a major health problem in the tropics. This infection has also been seen in north Queensland and WA traveler's returning from Bali.

A major issue in immunization in 2010 was the reactions to a particular brand of influenza vaccine, Fluvax<sup>TM</sup>, which resulted in many young children becoming unwell with fevers or in some cases febrile convulsions. As a result, the influenza vaccination program was ceased in Australia in young children. VTG responded rapidly and assisted the Health Department in gathering information and, in the laboratory, investigating the cause of the problems. This information was provided to the national authorities and eventually identified that the problems were restricted to one manufacturer's vaccine. This allowed the resumption of the influenza vaccine for children in July. Fluvax<sup>TM</sup> will not be used in young children under 5 in 2011 but other flu vaccines that have been shown to be safe will be available to protect children against influenza in 2011.

Middle ear infection (otitis media, OM) is the most common reason for a child to see a doctor, be given antibiotics, or undergo surgery. The health, social and financial costs of OM to Australia are substantial and treatment alone was

estimated to have cost \$390 million in 2008. We try to get a better understanding of why some children suffer from recurrent ear disease and others don't. To do this we study which bacteria and viruses are present in the nose and ears of children with OM and how the immune system functions in these children. We are developing new assays in the lab, collaborating with researchers around Australia and overseas and communicate our findings to colleagues and the general public.

A major highlight in 2010 for the OM research team (part of the Vaccine Trials Group) was the organization and successful execution of the inaugural Australian otitis media workshop (OMOZ) in 2010. This meeting brought together researchers and health care providers to discuss the science behind ear disease and plan our strategy for reducing the burden of ear disease in Australia. The outcomes from this meeting so far have included heightened media coverage to bring awareness of ear disease in Australia, particularly for Aboriginal children, as well as construction of an OMOZ website to keep the research community in touch. In 2010, we were awarded two NHMRC project grants to continue our OM research.

## Immunization

### 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. This study should be completed in 2012.

Funder of the project: Sanofi Pasteur SA

### A PHASE I/II STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF A VERO CELL-DERIVED WHOLE VIRUS H5N1 INFLUENZA VACCINE IN HEALTHY INFANTS, CHILDREN AND ADOLESCENTS AGED 6 MONTHS TO 17 YEARS

H5N1 influenza (flu) virus, also called the avian influenza virus, mainly infects birds, but can infect humans and cause severe disease. So far the numbers of humans infected in different parts of the world are low and the infection occurs mainly after direct contact with infected birds. However, a large portion of those humans infected with the H5N1 flu virus have been reported to have died.

The main purpose of this study is to determine the safety of the H5N1 vaccine and to see if the immune system produces special proteins called antibodies against the H5N1 flu virus strain in the vaccine.

Funder of the project: Baxter Innovations GmbH

### A PROSPECTIVE STUDY TO EVALUATE THE IMMUNOGENICITY OF TRIVALENT INACTIVATED INFLUENZA VACCINE IN CHILDREN (≥6 MONTHS TO ≤ 18 YEARS OF AGE) WHO ARE ON CANCER THERAPY

Dr Lyn Waring, Dr Peter Richmond, Dr Angela Alessandri, Prof. Catherine Cole, Dr Ushma Wadia, Dr Rishi Kotecha, Dr Thomas Walwyn

Influenza (the flu) is an easily spread disease caused by a virus, which most commonly causes fever, cough, breathing problems, runny/blocked nose, tiredness or irritability. Young children, the elderly and those on chemotherapy are more likely to be infected and are more likely to develop serious complications, which may require hospitalisation and even in rare cases death. It is recommended that those on cancer therapy should be given the flu vaccination every year. A cold can still develop despite being vaccinated. This is as a result of infection with either a different strain of the virus not covered by the vaccine, or not being able to produce protective antibodies to the three strains of the virus in the vaccine.

In this study, we are collecting information to see if children on cancer treatment are build up enough protection to stop them getting the flu after they have had the flu vaccine. We will do this by seeing if their immune system can make high enough levels of special proteins called antibodies against the flu virus.

Funder of the project: PMH Foundation Grant

**A PHASE 1/2A, RANDOMISED, DOUBLE-BLINDED, PLACEBO-CONTROLLED, DOSE- ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY AND VACCINE-LIKE VIRAL SHEDDING OF MEDI-534, A LIVE, ATTENUATED INTRANASAL VACCINE AGAINST RESPIRATORY SYNCYTIAL VIRUS (RSV) AND PARAINFLUENZA VIRUS TYPE 3 (PIV 3), IN HEALTHY 6 - <24 MONTH-OLD CHILDREN IN AND 2 MONTH OLD INFANTS**

Dr Peter Richmond, Dr Nicholas Conway; Dr Tanya Stoney

Respiratory Syncytial Virus (RSV) and Parainfluenza virus 3 (PIV3) are important causes of bronchiolitis (inflammation of the small airways in the lungs) and chest infections in infants and young children. The purpose of this study is to describe the safety, immune response (ability of the body to fight infection), and virus shedding (virus that can be found in the

nose after vaccination) of an experimental live PIV3 and RSV nasal vaccine called MEDI 534 in comparison to a placebo (an inactive sugar and salt solution that does not contain the vaccine, MEDI-534). MEDI -534 or placebo is given as nose drops in this study.

Funders of the project: MedImmune

**A PHASE III, OPEN RANDOMIZED, CONTROLLED, MULTI-CENTRE STUDY TO DEMONSTRATE THE NON-INFERIORITY OF THE MENINGOCOCCAL SEROGROUP C AND THE HAEMOPHILUS INFLUENZA 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 NO 106445 (PRIMARY PHASE) 106446,106449,106450,106452,106454 (LONG TERM FOLLOW UP)**

This trial commenced in 2006 with 49 toddlers being enrolled at the Vaccine Trials Group. The aim of the study was to evaluate the immune response and safety of a single dose of combined HibMenC vaccine when given to children at 12 months of age along with the MMR vaccine. To provide a comparison, a proportion of the children received the normal scheduled 12 month vaccines of separate MenC, Hib and MMR. The long term protection offered by these vaccines will be assessed for five years following the vaccination.

The rationale for producing combination vaccines is to decrease the number of actual needles the children will receive, while maintaining protection from vaccine preventable

diseases.

We are currently half way through the fourth year of the five year follow up with around 40 of the children still enrolled in the trial.

Funders of the Project: GlaxoSmithKline Biologicals

**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, 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 fifth year of the Cervarix HPV vaccine trial for women aged over 26 years commenced in 2009. 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.

Funder of the project. GlaxoSmithKline Biologicals

## 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 if a woman was pregnant at

her last HPV-008 study visit and no cervical sample was taken at that visit was also eligible to enter. Nineteen women were eligible to participate in this study which began in 2009.

Funder of the project: GlaxoSmithKline Biologicals

## A PHASE IIIB, OPEN, MULTI CENTRE GYNAECOLOGICAL EXTENSION STUDY FOR THE FOLLOW-UP OF A SUBSET OF HPV-015 STUDY SUBJECTS

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. 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 if a woman was pregnant at her last HPV-008 study visit and no cervical sample was taken at that visit was also eligible to enter. Currently no women are eligible to participate in this study.

Funder of the project: GlaxoSmithKline Biologicals

## A PHASE IIIB, OPEN-LABEL, MULTI-CENTRE IMMUNIZATION STUDY TO EVALUATE THE SAFETY OF GLAXOSMITHKLINE (GSK) BIOLOGICALS' HPV-16/18 L1 VLP AS04 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. Currently only four women are eligible for this study.

Funder of the project: GlaxoSmithKline Biologicals

## A PHASE IIA RANDOMIZED, DOUBLE BLIND, CONTROLLED WITH GARDASIL™ CLINICAL TRIAL TO STUDY THE TOLERABILITY AND IMMUNOGENICITY OF V505 [A MULTIVALENT HUMAN PAPILOMAVIRUS [HPV] L1 VIRUS-LIKE PARTICLE [VLP] VACCINE) IN HEALTHY 16 TO 26 YEAR OLD WOMEN

Associate Professor Peter Richmond

Currently there are two HPV vaccines available that prevent infection of some HPV types:

1. GARDASIL® a vaccine developed by Merck Sharp & Dohme (Australia) Pty. Ltd. and manufactured by CSL. This vaccine provides protection against HPV types 6, 11, 16 & 18 and is currently available free for girls and women aged 9 to 26 years. GARDASIL® will be used as the 'Control' vaccine in this study.
2. Cervarix\*, developed by GlaxoSmithKline, provides protection against the infection of HPV types 16 & 18.

Merck Sharp & Dohme (Australia) Pty. Ltd. has developed a new vaccine called V505 which is designed to protect against 9 different types of HPV infection with are responsible for about 90 per cent of cervical cancers and 90 percent of genital warts. This vaccine is similar to the GARDASIL® in that it contains proteins called VLPs that resemble different types of HPV to the body's immune system, but are not actually viruses. This is the first time this study vaccine (V505) has been tested in

humans, however a vaccine with eight (8) of the VLPs has been tested in people and found to be generally well tolerated.

This study has been ongoing since 2007 and 25 subjects were recruited at this site. Completion for this study is due in 2011.

Funder of the project: Merck Sharp & Dohme

#### IMMUNOGENICITY AND SAFETY OF ACELLULAR PERTUSSIS VACCINE GIVEN AT BIRTH IN HEALTHY INFANTS.

Associate Professor Peter Richmond

Currently, vaccines to protect against Pertussis (whooping cough) are given from 2 months of age, but almost one third of infant hospitalisations for Pertussis occur prior to 2 months. This study aims to randomly assign a group of newborn infants to birth acellular Pertussis (Pa) vaccine versus current standard practice. Infants will either receive a Pa-containing vaccine at birth and then 6 weeks, four and six months of age or the standard schedule with the first dose given at 6 rather than 8 weeks. Antibody responses in the blood, which are believed to correlate with protection, will be compared at 6 weeks, 10 weeks, 6 months and 8 months of age.

This study aims to show whether earlier vaccination gives better protection from Pertussis at the time when babies are most likely to die from this infection.

This study is also being conducted in Adelaide, Melbourne and Sydney. We aim to enrol 440 babies nationally (110 in Perth) and we have so far enrolled 193 babies (55 in Perth). We aim to complete enrolment by the end of July 2011.

Funder of the project: National Health and Medical Research Council (NHMRC).

#### A PHASE 1 TRIAL TO EVALUATE THE SAFETY, TOLERABILITY AND IMMUNOGENICITY OF 3 ASCENDING DOSE LEVELS OF A 3- ANTIGEN STAPHYLOCOCCUS AUREUS VACCINE (SA3AG) IN HEALTHY ADULTS

Associate Professor Peter Richmond

Staphylococcus aureus (Staph) is a bacterium (germ) that inhabits the skin and mucous membranes throughout life. Staph infection can cause pneumonia, skin, and wound infections. The success of antibiotics in the prevention and treatment of staph infection has been limited by the rapid and widespread emergence of antibiotic-resistant strains.

This vaccine to prevent staph infections (SA3Ag) is being studied for the first time in man. The study is evaluating three different dose levels of the SA3Ag vaccine to see how if the vaccine is safe and how soon it offers protection against staph infection.

The study is expected to finish in July 2011.

Funder of project: Wyeth Australia Pty Ltd / Pfizer Australia and New Zealand

#### A RANDOMIZED, SINGLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 TRIAL OF THE SAFETY, IMMUNOGENICITY, AND TOLERABILITY OF MENINGOCOCCAL SEROGROUP B (MNB) RLP2086 VACCINE AT DOSES OF 60 µg, 120 µg, AND 200 µg IN HEALTHY ADOLESCENTS AGED 11 TO 18 YEARS

Associate Professor Peter Richmond

The purpose of this study is to collect information about how safe the Meningococcal B (rLP2086) vaccine is in healthy adolescents aged 11-18 years of age. This Meningococcal B vaccine is new but has been used in previous studies in adults and children. In this study, some of the ingredients in the vaccine have changed so that the vaccine can be made more easily.

This is the second time the vaccine will be administered to

adolescents and this study will evaluate the immune response of adolescents to the vaccine and examine the safety of the vaccine.

Stage 1: The aim of this study was to evaluate the safety, tolerability and immune response of the investigational Meningococcal B vaccine in adolescents aged 11 – 18 years. In order to evaluate the Meningococcal B vaccine some adolescents/young adults will be given a placebo vaccine.

The Meningococcal B vaccine was evaluated at three dose levels. The Vaccine Trials Group enrolled 77 participants in stage 1.

Stage 2: Participation in Stage 2 will last up to 3 ½ years. Subjects who received specific dose levels and placebo were invited to participate in stage 2. Stage 2 aims to continue to evaluate the vaccine's ability to produce long term protection to Meningococcus B disease. Vaccine Trials Group enrolled 33 participants in stage 2.

Funder of project: Wyeth Australia Pty Ltd / Pfizer Australia and New Zealand

## Surveillance

#### THE CHILDREN'S WESTERN AUSTRALIAN INFLUENZA VACCINE EFFECTIVENESS (WAIVE) STUDY

Associate Professor Peter Richmond, Dr Dale Carcione, Dr Gabriela Dixon, Dr Paul Effler,

Associate Professor Gary Geelhoed, Dr Anthony Keil, Dr Heath Kelly, Dr Alan Leeb, Hannah Moore

Dr David Smith, Dr Paul Van Buynder, Simon Williams, Peter Jacoby

The main objectives of the project are 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). After obtaining parent consent we complete an initial questionnaire at the time of recruitment and collect two nasal swabs (one from each nostril), these are then sent to our pathology department to be tested for influenza. Parents are given a second questionnaire to take home and complete 7-10 days after onset of child's illness. Approximately a week after recruitment parents are given a follow up phone call with the results of the nasal swabs.

This study is seasonal and usually starts anywhere from June/July and usually winds up October/November (depending on the flu season). We have a friendly team of research assistants working in our emergency department in the evenings and weekends. They can be recognized by their blue T shirts adorned with the WAIVE logo.

Funder of the project: Communicable Disease Control Directorate, Department of Health WA

## ROTAVIRUS AND GASTROENTERITIS SURVEILLANCE STUDY (RAGS)

Associate Professor Peter Richmond, Dr Paul Effler, Dr Dale Carcione, Prof David Forbes,

Associate Professor Gary Geelhoed, Dr Gerald Harnett, Dr Anthony Keil, Associate Professor Carl Kirkwood, Professor Tom Riley, Dr David Smith, Dr Michael Watson, Simon Williams

This study aims 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 immunization 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. A stool sample is required, and will be collected at time of recruitment. The stool sample is then sent to the pathology department for testing. Parents are contacted approximately one week after recruitment with the pathology result and to see when child's diarrhoea and vomiting ceased.

Funder of the project: Department of Health WA

## PAEDIATRIC ACTIVE ENHANCED DISEASE SURVEILLANCE - PAEDS

Investigators: Richmond P, 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, 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 three conditions currently included as surveillance studies are: Acute Flaccid Paralysis (AFP), Intussusception and Varicella. Research nurses identify children with the conditions under surveillance and after obtaining consent from the parents; the nurses collect clinical data and

biological specimens from cases, along with information on risk factors, vaccination history, management and short term outcomes. PAEDS assists with reporting to appropriate bodies such as ADRAC or CDCD to improve reporting rate. Biological samples for AFP, Varicella and Intussusception are collected and forwarded to appropriate reference laboratories.

Funders of the project: Commonwealth Dept of Health & Ageing

## THE WESTERN AUSTRALIAN CHILDREN'S FOLLOW UP AND ACTIVE SURVEILLANCE OF TRIVALENT INFLUENZA VACCINE (FAST) STUDY

Associate Professor Peter Richmond, Associate Professor Christopher Blyth, Dr Nicholas Conway

Summary of Project

Western Australia is the only Australian state providing free immunisation with trivalent inactivated influenza vaccine (TIV) for preschool-aged children 6 months to 5 years of age. Safety concerns were raised during the 2010 TIV program in Australia after an apparent increase in adverse events following immunisation. Increased numbers of children presenting to Perth's major paediatric hospital with severe febrile reactions post-TIV were noted, a number of whom developed febrile convulsions. The Western Australian paediatric influenza vaccination program and national influenza immunisation programs for children less than 5 years of age were temporarily suspended pending further investigation.

All febrile convulsions occurred following administration of Fluvax® or Fluvax Junior® which were subsequently withdrawn from the childhood immunisation program prior to resumption of the 2010 campaign. The Western Australian paediatric influenza vaccination program will continue in 2011 using a combination of Influvac®, Vaxigrip® and Agrippal.

The FAST study has been designed to detect any significant

increase in seasonal TIV related febrile reactions and/ or any other adverse events following immunisation with seasonal TIV. It will also provide timely feedback to healthcare consumers regarding the rate of TIV associated adverse events.

Randomized selection of subjects will be contacted by telephone following vaccination to enquire of any complications. De-identified results will be published and readily accessible (in an electronic format) to healthcare providers, vaccine manufacturers and consumers.

Funder of project: Communicable Disease Control Directorate, Health Protection Group, Western Australian Department of Health (WA DoH)

## Infectious Disease

### AN OPEN-LABEL, MULTI-CENTRE, SINGLE ARM STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS ZANAMIVIR IN THE TREATMENT OF HOSPITALISED ADULTS, ADOLESCENTS AND PAEDIATRIC SUBJECTS WITH CONFIRMED INFLUENZA INFECTION

Associate Professor Chris Blyth and Associate Professor Peter Richmond

There are currently no intravenous influenza (flu) antiviral agents approved for use in patients with severe flu. The purpose of this study is to test the safety and effectiveness of a new intravenous form of zanamivir in adults and children with severe flu. Zanamivir is usually given to patients who have the flu, using a puffer. The study commenced in 2010 and due to a quieter than usual flu season no one was enrolled into the study. The study will be ongoing in 2011.

### DYNAMICS OF HAEMOPHILUS HAEMOLYTICUS AND NONTYPEABLE HAEMOPHILUS INFLUENZAE COLONISATION IN OTITIS-PRONE CHILDREN

Dr Lea-Anne Kirkham and Dr Selma Wiertsema

Ear infections (OM) are predominantly caused by nontypeable Haemophilus influenzae (NTHi). Aboriginal children have the highest NTHi OM rates in the world. A vaccine has been introduced to Australia to reduce NTHi carriage and OM. H. haemolyticus (Hh) masquerades as NTHi leading to inaccurate surveillance of NTHi carriage. This project will document true NTHi and Hh carriage rates in OM-prone children, to guide national vaccine policy and set a benchmark for assessing the impact of OM-targeted vaccines in Australian children.

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 Selma Wiertsema and Dr Lea-Anne Kirkham

We and others have shown that children with ear infections (OM) have a good immune response against the pneumococcus which causes OM, however, these children still get sick. 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 will use 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.

Funder of the project: National Health and Medical Research Council (NHMRC).

### THE ROLE OF BACTERIAL BIOFILM AND INTRACELLULAR INFECTION IN CHRONIC AND RECURRENT OTITIS MEDIA

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 being 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 in 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.

## Human Immunology

### IDENTIFYING THE CELLULAR MECHANISMS THAT PROMOTE EFFECTIVE MENINGOCOCCAL VACCINE RESPONSES IN INFANTS

Angela Fuery, Associate Professor Peter Richmond and Dr

## Andrew Currie

Polysaccharide-encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* are capable of causing devastating disease such as Meningitis and Septicaemia. Glyco-conjugate vaccines, which consist of the polysaccharide capsule of these bacteria joined to a carrier protein, have been very successful in reducing the amount of disease caused by these bacteria. Despite their success, very little is known about the exact mechanisms of these vaccines.

Our study is investigating a cohort of Infants who received a combined *Haemophilus influenzae* B, Meningococcal C and Y glyco-conjugate vaccine (HibMenCY). Analysis of cells and antibodies obtained from these infants at various time points pre and post-vaccination will help us to determine what factors influence generation of a more effective and long-lasting immune response. In doing this, it is hoped that we will be able improve vaccination against Meningococcal bacteria, and other polysaccharide-encapsulated bacteria.

## INFECTION AND IMMUNITY IN THE HUMAN NEWBORN

Dr Andrew Currie, Associate Professor Peter Richmond, Professor Karen Simmer, Associate Professor David Burgner, Dr Tobias Strunk, Dr Dorota Doherty, Dr Ofer Levy

Our "PREDICT" study is the first of its kind in the world to follow the development of the newborn immune system in extremely premature infants over the first weeks of their life, and to look for predictors of infection. We have recruited over 104 extremely preterm infants so far, with only 16 more to go. We have generated a large amount of data to date and are now seeking database experts to help us get every drop of information out of the study.

Preterm babies (→22,000/yr in Australia) are among the most vulnerable members of our society and commonly get serious blood infections in the first few weeks of life. However, we

know very little about why this is so. Through two nationally funded studies (PREDICT and SPIN) we have been examining how the immune system of preterm babies develop after birth, to see if this can explain the increased risk of infection and even predict which babies are likely to get sick.

This has been challenging work – delivery times are unpredictable, our participants are very small with small blood volume and require intensive care, not to mention that their parents are naturally stressed at this time. However, thanks to the tireless work of the PREDICT team at VTG (Julie Hibbert and Amy Prosser) and at KEMH (Kok ChooiHeen) we have had a busy and productive year, recruiting 104 out of 120 very preterm infants and collecting samples over the first 4 weeks of life. We have also recruited healthy term babies with samples at birth and 4 weeks later (thanks to Lisa Montgomery at VTG) which will help us understand normal infant development.

We have started to analyse the first data from these studies and results look promising. We are aiming to complete recruitment and data analysis in 2011 and start making serious inroads into understanding and preventing infections in preterm infants.

Funders of the project: National Health and Medical Research Council (NHMRC), BrightSpark Foundation, European Society for Infectious Diseases

## 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  
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

Sanela Bilic MBA BSc  
Associate Professor Christopher Blyth MBBS (Hons) DCH FRACP FRCPA  
Karli Geerlings BSc (Hons)  
Nicholas Conway MBChB MRCPCH MPH  
Andrew Currie PhD BSc (Hons)  
Samantha Curtis BSc (Hons)  
Jennifer Ebsary DipN RM  
Camille Gibson BSc Environmental Health RM BSc Nursing  
Julie Hibbert BSc (Hons) MSc  
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Jane Jones BSc (Hons) BScN DipHealth Sc  
Jan Jones BSc (Hons) DipEd  
Jennifer Kent DipN  
Lea-Ann Kirkham PhD BSc (Hons)  
Fiona MacDonald BSc RM RGN  
Lisa Montgomery  
Jennifer Morrison RN RM  
Eva Mowe BSc (Hons)  
Shalene Nandlall Dip Nursing Sc and Midwifery

Annemarie Naylor Grad Cert CTM  
Amy Prosser BSc (Hons)  
Karen Riley BSc  
Alison Roberts Post Grad Dip Health Promotions BSc Dip Health Sci  
Christine Robins EN  
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Rachel Skinner MBBS PhD FRACP  
Jason Tan MBBS  
Nichola Taylor Dip HE BSc (Hons)  
Selma Wiertsema PhD MScBSc  
Melissa Whinnen BSc (Hons)  
Ushma Wadia MBBS

#### POSTGRADUATE STUDENTS

Angela Fuery BSc (Hons) PhD Candidate  
Ruth Thornton BSc (Hons) PhD Candidate

#### RESEARCH SUPPORT

Robin Fowler  
Jennifer Nash-Wilcox  
Chantelle Ruoss  
Su-Lin Chan  
Chiara Kinder  
Thel Khin Hla  
Gabrielle Sicari  
Sophie Reynolds  
Samantha Moore  
Patrick Thornton

#### Awards

Angela Fuery, University of Western Australia Award, Australian Society for Medical Research (WA branch), June 2010

Selma Wiertsema, PHAA early career researcher

Ruth Thornton, Best poster prize. Frontiers 2010: The Art, Science and Future of Otorhinolaryngology.

Christopher Blyth, Travelling Scholarship: 50th ICAAC Meeting, Boston, USA 2010, Australian Society for Antimicrobials and AstraZeneca Australia

### External Committees

#### INTERNATIONAL

World Health Organisation Western Pacific Region Workshop on National Immunisation Technical Advisory Groups. Seoul, Korea

#### NATIONAL

Deputy Chair, Australian Technical Advisory Committee on Immunisation (ATAGI), Commonwealth Dept. of Health and Ageing

Chair, ATAGI MMR-Varicella and Herpes Zoster Vaccine Working Party

Member, ATAGI Pneumococcal Vaccine Working Party,

Member, ATAGI Hib and meningococcal C Vaccine Working Party

Member, ATAGI H1N1 Influenza Vaccine Working Party,

Member, ATAGI Influenza Vaccine Adverse Event Working Party,

Organising Committee Public Health Association of Australia 12th National Immunisation Conference, Adelaide August 2010

Adelaide Women's and Children's Hospital Paediatric Trials Unit Scientific Advisory Board

National Centre for Immunisation research and Surveillance

Scientific Advisory Board 2008 to present

Rotavirus vaccine (RV3) Phase 1-2 studies Data Safety Monitoring Board, Murdoch Children's Research Institute, Melbourne

National Immunisation Strategy Forum

National Medicine Policy forum (ATAGI representative)

Christopher Blyth, WSPID Conference, Melbourne 2011, World Society for Pediatric Infectious Disease

Christopher Blyth, Organising Committee: ASID Conference, Perth 2012, Australian Society for Infectious Diseases

Christopher Blyth, Australian and New Zealand Mycology Interest Group Business Committee

Australian Society for Infectious Diseases

Selma Wiertsema. GlaxoSmithKline: pneumococcal vaccination group.

Lea-Ann Kirkham and Selma Wiertsema. OMOZ scientific organising committee

Lea-Ann Kirkham and Selma Wiertsema. Australian Society for Immunology, Infection and Immunity workshop, scientific organising committee.

Ruth Thornton. OMOZ scientific organising committee

#### LOCAL

Christopher Blyth, WA Tuberculosis Advisory Council, Health Department of Western Australia

Christopher Blyth, Expert Advisory Committee for Prevention and Control of Pertussis in WA, Health Department of Western Australia

Angela Fuery. Australasian Society for Immunology (WA Branch) Student committee. April 2008-present.

## WA Immunisation Scientific Advisory Group 2006

Expert Advisory Committee for Prevention and Control Of Pertussis in WA 2010

Princess Margaret Hospital for Children Clinical Staff Association Executive

Princess Margaret Hospital for Children Ethics Committee

Princess Margaret Hospital for Children Medical Advisory Committee

New Children's Hospital Research and Education Reference group (Chair)

Child Health Research and Education Advisory Committee, Child and Adolescent Health Services

Vaccines: why we need them and how they work. World Immunology Day, SciTech, West Perth

## Invited Presentations

Lea-Ann Kirkham. Molecular detection of pathogens that cause pneumonia. PNG pneumonia colloquium, Goroka, Papua New Guinea, August 2010.

Lea-Ann Kirkham. Lectures on pneumococcal disease and otitis media to Biomedical Science students at Murdoch University. September 2010

Selma Wiertsema. Protection against bacterial infection in children with recurrent otitis media. Australian Society for Immunology; Infection and Immunity workshop, December 2010

Selma Wiertsema. Understanding Otitis Media in Infants and toddlers. Telethon Institute for Child Health Seminar Series. June 2010

Otitis media Research: Where to now? The Inaugural OMOZ

## Workshop, Darwin, May 2010

Meningococcal vaccines in Australia: what have they done and what can we expect? Amanda Young Foundation 3rd Meningococcal Conference, Perth August 2010

Perspective on Future Vaccines for Prevention of Acute Respiratory Infection Papua New Guinea Medical Symposium, Colloquium on Pneumonia, Goroka, PNG, August 2010

The Introduction of Pandemic H1N1 09 Influenza Vaccine in Australia: Trials and tribulations. Public Health Association of Australia 12th National Immunisation Conference, Adelaide August 2010

Targeting adolescents with meningococcal vaccines. Public Health Association of Australia 12th National Immunisation Conference, Adelaide August 2010

Understanding adjuvants: innovations for new vaccines. Public Health Association of Australia 12th National Immunisation Conference, Adelaide August 2010

Making vaccine policy decisions. Public Health Association of Australia 12th National Immunisation Conference, Adelaide August 2010

Chairperson. Global and Regional Issues in Immunisation Public Health Association of Australia 12th National Immunisation Conference, Adelaide August 2010

Safety and Immunogenicity of Serogroup B Neisseria meningitidis (MnB) rLP2086 Vaccine in Adults and Adolescent Subjects: Overview of 3 Clinical Trials International Pathogenic Neisseria Conference, Banff, Canada September 2010

Australian Technical Advisory Group on Immunisation – making vaccine policy in Australia. World Health Organisation Western Pacific Region Workshop on National Immunisation Technical Advisory Groups. Seoul, Korea November 2010

## Publications

Blyth CC, Middleton PG, Harun A, Sorrell TC, Meyer W, Chen SCA. Clinical associations and prevalence of *Scedosporium* spp. in Australian cystic fibrosis patients: identification of novel risk factors. *Medical Mycology* 2010; 48(Suppl 1), S37-44.

Wang B, Dwyer DE, Blyth CC, Soedjono M, Shi H, Kesson A, Ratnamohan M, McPhie K, Cunningham AL, Saksena NK. Detection of the rapid emergency of the H274 mutation associated with oseltamivir-resistance in severe pandemic influenza virus A/H1N1 09 infections. *Antiviral Research* 2010; 87(1): 16-21.

Blyth CC, Gomes L, Sorrell TC, da Cruz M, Sud A, Chen SCA. Skull base osteomyelitis: Fungal versus Bacterial Infection. *Clinical Microbiology and Infection*: 2010 Apr 2. DOI: 10.1111/j.1469-0691.2010.03231.x.

Blyth CC, Foo H, van Hal SJ, Hurt AC, Barr IG, McPhie K, Armstrong PK, Rawlinson WD, Sheppard V, Conaty S, Staff M, Dwyer DE. Complexity of Influenza Outbreaks during the World Youth Day 2008 Mass Gathering and its Impact on Community Seasonal Influenza Activity. *Emerging Infectious Diseases* 2010; 16(5): 809-15.

Blyth CC, Hale KA, Palasanthiran P, O'Brien TA, Bennett MH. Antifungal therapy in infants and children with proven, probable or suspected invasive fungal infections (Review). *Cochrane Database of Systematic Reviews*. 2010; Feb 17;2:CD006343.

Blyth CC, Harun A, Middleton PG, Sleiman S, Lee O, Sorrell TC, Meyer W, Chen SCA. Detection of occult *Scedosporium* species in respiratory tract specimens in cystic fibrosis (CF) by use of selective media. *Journal of Clinical Microbiology* 2010; 48(1): 314-316. (IF = 4.162; CI = 5)

Kok J, Blyth CC, Foo H, Patterson J, Taylor J, McPhie K, Ratnamohan VM, IRedell JR, Dwyer DE. Comparison of a rapid antigen test with nucleic acid testing during cocirculation of

pandemic influenza A/H1N1 09 and Seasonal influenza A/H3N2. *Journal of Clinical Microbiology* 2010; 48(1): 290-291.

Currie, A.J., S. Curtis, T. Strunk, K. Riley, K. Liyanage, S. Prescott, D. Doherty, K. Simmer, P. Richmond, D. Burgner. Preterm infants have deficient monocyte and lymphocyte cytokine responses to group B streptococcus. *Infection & Immunity*. Accepted Jan 21st 2011

Strunk T, P. Richmond, A. Prosser, K. Simmer, O. Levy, D. Burgner and A. Currie. Method of bacterial killing differentially affects the human innate immune response to *Staphylococcus epidermidis*. 2010. *Innate Immunity*. Accepted 7th July 2010. doi: 10.1177/1753425910379840.

Strunk T\*, M. Coombs\*, A. Currie, P. Richmond, D. Golenbock, L. Stoler-Barak, L. Gallington, M. Otto, D. Burgner, and O. Levy. (2010). TLR2 Mediates Recognition of Live *Staphylococcus Epidermidis* and Clearance of Bacteremia. *PLoS ONE* 5(4): e10111.

Strunk, T., Currie, A., Richmond, P., Simmer, K. and Burgner, D. (2011). Innate immunity in human newborn infants: prematurity means more than immaturity. *The Journal of Maternal-Fetal & Neonatal Medicine*. 24(1): 25-31

Strunk, T. Doherty D., Jaques A., Simmer, K., Richmond, P., Kohan R., Charles, A. and Burgner D. Histologic chorioamnionitis is associated with reduced incidence of late-onset sepsis in very preterm infants. 2011. Under review by *Journal of Paediatrics*.

Howman RA, Charles A, Jacques A, Doherty D, Simmer K, Strunk T, Richmond P, Cole C, Burgner D. Maternal, umbilical cord and neonatal inflammatory and hematologic markers in histologic chorioamnionitis. 2011. Under review by *Am J Obstet Gyn*.

McDonnell, A.M., Robinson, B.W.S. and Currie A.J. (2010). Tumor Antigen Cross-Presentation and the Dendritic Cell: Where it All Begins? *Clinical and Developmental Immunology*.

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Nolan T, Richmond P, Marshall H, McVernon J, Alexander K, Mesaros N, Aris E, Miller J, Poolman J, Boutriau D. Immunogenicity and safety of a combined *Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate (HibMenCY-TT) vaccine in infants *Pediatric Infectious Diseases Journal* 2011; 30:190-196 (Impact factor 2.854).

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W, Francis RW, Ang W, Pennell CE Burgner D, Richmond P, Vijayasekaran S, Coates HL, Brown SD, Blackwell JM, Jamieson SE. FBXO11, a regulator of the TGF $\beta$  pathway, is associated with severe otitis media in Western Australian children. *Genes and Immunity* 2011 Feb 3. [Epub ahead of print] [Impact factor 4.222]

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Dixon G, Moore HC, Kelly H, Jacoby P, Carcione D, Williams S, Smith D, C Keil AD, van Buynder P, Richmond P and the WAIVE study team. Assessing the protective effect of influenza vaccine against laboratory confirmed influenza in hospitalised children aged 6-59 months: the first year of the WAIVE study *Influenza and other Respiratory Viruses* 2010 4:231-234 (Impact factor 1.754)

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Thornton R & Coates H. Chronic mucosal disease and the role of intracellular infection and biofilm. In: Sih T, Chinski A, Eavey R, Godinho R, editors. IX IAPO - Manual of Pediatric Otorhinolaryngology. Sao Paulo: Editora e Grafica Vida & Consciencia; 2010. p. 211-215. (Invited chapter).

### Letters and Case Reports

Blyth CC, Hale KA, Palasanthiran P, O'Brien TA, Bennett MH. Antifungal therapy in infants and children with proven, probable or suspected invasive fungal infections. *Evidence-Based Child Health: A Cochrane Review Journal* 2010; 5(4); 2001-2006

## Peer Reviewed Conference Abstracts (Oral presentations\*)

Blyth CC, Webb SA, Kok J, Iredell JR, ANZIC Influenza Investigators and COSI Microbiology Investigators. Bacterial and Viral Coinfections in Severe Influenza Infection 2009. Interscience Conference on Antimicrobials Agents and Chemotherapy, Boston 2010.

Kok J, Blyth CC, Foo H, Tudo K, Heuston L, Iredell JR, Dwyer DE. Seroprevalence of Pandemic (H1N1) 2009 Influenza in HIV-infected Individuals. Interscience Conference on Antimicrobials Agents and Chemotherapy, Boston 2010.

Kok J, Blyth CC, Foo H, McPhie K, Ratnamohan VM, O'Sullivan MV, Iredell JR, Dwyer DE. Age and Respiratory Tract Sample Type Affect Performance of Antigen Tests in Detecting Pandemic (H1N1) 2009 Influenza. Australasian Society of Infectious Diseases Conference, Darwin 2010.

\*Ong AT, Bency R, Blyth CC, Vicaretti M, Harun A, Meyer W, Gilroy N, Chen SCA. Fatal mycotic aneurysms due to *Scedosporium apiospermum*. ECMM-ISHAM Working Group *Pseudallescheria/Scedosporium*, Bonn 2010.

\*Chen SCA, Blyth CC, Harun A, Sorrell TC, Meyer W, Middleton P. Clinical associations of *Scedosporium* in cystic fibrosis. ECMM-ISHAM Working Group *Pseudallescheria/Scedosporium*, Bonn 2010.

Ong AT, Bency R, Blyth CC, Vicaretti M, Harun A, Meyer W, Gilroy N, Chen SCA. Fatal mycotic aneurysms due to *Scedosporium apiospermum*. European Congress of Clinical Microbiology and Infectious Diseases, Vienna 2010.

\*Kok J, Blyth CC, Foo H, Iredell JR, Dwyer DE. Performance characteristics of a rapid antigen test and immunofluorescent antibody test compared with nucleic acid testing in pandemic (H1N1) 2009 influenza. Multinational Influenza Seasonal Mortality Study Oceania Regional Meeting and Workshop, Melbourne 2010.

191 publications in 2010

1. Abeywardana S, Bower C, Halliday J, Chan A, Sullivan EA. Prevalence of neural tube defects in Australia prior to mandatory fortification of bread-making flour with folic acid. *Australian and New Zealand Journal of Public Health* 2010;34:351-55.
2. Alfonso HS, Reid A, de Klerk NH, Olsen N, Mina R, Ambrosini GL, Beilby J, Berry G, Musk BA. Retinol supplementation and mesothelioma incidence in workers earlier exposed to blue asbestos (Crocidolite) at Wittenoom, Western Australia. *European Journal of Cancer Prevention* 2010;19:355-59.
3. Ambrosini GL, Huang RC, Mori TA, Hands BP, O'Sullivan TA, de Klerk NH, Beilin LJ, Oddy WH. Dietary patterns and markers for the metabolic syndrome in Australian adolescents. *Nutrition, Metabolism and Cardiovascular Diseases* 2010;20:274-83.
4. Attia J, Thakkinstian A, McElduff P, Milne E, Dawson S, Scott RJ, de Klerk N, Armstrong B, Thompson J. Detecting genotyping error using measures of degree of Hardy-Weinberg disequilibrium - art. no. 5. *Statistical Applications in Genetics and Molecular Biology* 2010;9:5-5.
5. Bailey HD, Armstrong BK, de Klerk NH, Fritschi L, Attia J, Lockwood L, Milne E. Exposure to diagnostic radiological procedures and the risk of childhood acute lymphoblastic leukemia. *Cancer Epidemiology, Biomarkers and Prevention* 2010;19:2897-909.
6. Bailey HD, Milne E, de Klerk N, Fritschi L, Bower C, Attia J, Armstrong BK. Representativeness of child controls recruited by random digit dialling. *Paediatric and Perinatal Epidemiology* 2010;24:293-302.
7. Bebbington A, Percy A, Christodoulou J, Ravine D, Ho G, Jacoby P, Anderson A, Pineda M, Ben Zeev B, Bahi-Buisson N, Smeets E, Leonard H. Updating the profile of C-terminal MECP2 deletions in Rett syndrome. *Journal of Medical Genetics* 2010;47:242-48.
8. Beesley AH, Rampellini JL, Palmer ML, Heng JY, Samuels AL, Firth MJ, Ford J, Kees UR. Influence of wild-type MLL on glucocorticoid sensitivity and response to DNA-damage in pediatric acute lymphoblastic leukemia. *Molecular Cancer* 2010;9:284.
9. Beilby J, Ambrosini GL, Rossi E, de Klerk NH, Musk AW. Serum levels of folate, lycopene, beta-carotene, retinol and vitamin E and prostate cancer risk. *European Journal of Clinical Nutrition* 2010;64:1235-38.
10. Berry LJ, Sheil B, Garratt L, Sly PD. Stability of interleukin 8 and neutrophil elastase in bronchoalveolar lavage fluid following long-term storage. *Journal of Cystic Fibrosis* 2010;9:346-50.
11. Berry RJ, Bailey L, Mulinare J, Bower C. Fortification of flour with folic acid. *Food and Nutrition Bulletin* 2010;31:S22-35.
12. Bertram CM, Hawes SM, Egli S, Peh SL, Dottori M, Kees UR, Dallas PB. Effective adenovirus-mediated gene transfer into neural stem cells derived from human embryonic stem cells. *Stem Cells and Development* 2010;19:569-78.
13. Biros E, Cooper M, Palmer LJ, Walker PJ, Norman PE, Golledge J. Association of an allele on chromosome 9 and abdominal aortic aneurysm. *Atherosclerosis* 2010;212:539-42.
14. Bittles AH, Glasson EJ. Increased longevity and the comorbidities associated with intellectual and developmental disability. In: Bax M, Gillberg C, editors. *Comorbidities in Developmental Disorders*. London: Mac Keith Press; 2010. p. 125-41.
15. Blair E. Individualised growth curves and size at birth In: Symonds M, Ramsay M, editors. *Maternal-fetal nutrition during pregnancy and lactation*. New York: Cambridge University Press; 2010. p. 34-39.
16. Blair E. Epidemiology of the cerebral palsies. *Orthopedic Clinics of North America* 2010;41:441-55.
17. Bower C, Milne E. Colon cancer in Chile. *European Journal of Gastroenterology and Hepatology* 2010;22:900.
18. Bower C, Rudy E, Callaghan A, Quick J, Nassar N. Age at diagnosis of birth defects. *Birth Defects Research Part a-Clinical and Molecular Teratology* 2010;88:251-55.
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20. Boyle T, Shepherd CCJ, Pearson G, Monteiro H, McAullay D, Economo K, Stewart S. Awareness and impact of the 'Bubblewrap' advertising campaign among Aboriginal smokers in Western Australia. *Tobacco Control* 2010;19:83-86.
21. Brinkman SA, Johnson SE, Lawrence D, Codde JP, Hart MB, Straton JA, Silburn S. Study protocol for the evaluation of an Infant Simulator based program delivered in schools: a pragmatic cluster randomised controlled trial. *Trials* 2010;11:100.
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