



Our future

*Research to improve the
health and wellbeing of children*



PREVENTION
INNOVATION
DEDICATION

Annual Report **2007**

Telethon Institute for Child Health Research

Who we are

The Telethon Institute for Child Health Research is Western Australia's only research facility dedicated to child health. Like the childhood illnesses and diseases we investigate, our team is diverse, consisting of some of Australia's, and the world's, leading experts in their fields.

We are housed in a purpose-built research facility on the edge of the Perth CBD and have close to 450 staff and students as well as around 70 honorary and visiting researchers throughout the year.

The Institute is a non-Government, not-for-profit organisation with strong affiliations with the State children's hospital and all the major WA universities.

What we do

Our focus is on children, young people and their families.

We investigate the most complex, costly and devastating health problems facing our children in the 21st century. We approach these problems with dedication and innovation as we try to achieve our overall goal - prevention.

We work together. We work with others. We work hard to improve the life chances for all children.

You will find information about our broad range of research programs in the following pages.

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.

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*“Children are one third
of our population and
all of our future.”*

Select Panel for the Promotion of
Child Health, 1981

New Division of Genetics and Health

The Institute's new Division of Genetics and Health was formed in 2007 when Professor Jenefer Blackwell and her team were recruited from Cambridge in the UK. The team includes Senior Research Fellow Christopher Peacock, Research Fellow Sarra Jamieson, and Bioinformatician Richard Francis. For Jenefer, a graduate of UWA, the return to Perth fulfils a long-held dream to come home. For Christopher, Sarra and Richard, the move to Australia is an exciting new adventure.

The primary aim of the new Division is to build capacity to enable genetics to be applied as a tool in epidemiological studies that underpin much of the research of the Institute. Following the human genome project, genome-wide approaches to measuring human genetic variation has emerged as a powerful tool in understanding both genetic and modifiable environmental risk factors for disease. Specific projects in the new Division will build initially on the groups previous interests in genetic susceptibility to infectious diseases.

Jenefer completed her PhD in Population Genetics at UWA in 1974, then headed overseas for postdoctoral research at the London School of Hygiene and Tropical Medicine. There she established a career in tropical medical research, focusing largely on genetic studies of susceptibility to infections such as toxoplasmosis (a parasitic infection that can cause stillbirth or miscarriage in pregnant women as well as eye or brain disease in congenitally infected babies) and leishmaniasis (a major parasitic disease of the tropics that is transmitted by the bite of the sandfly). It was during her time in London that Jenefer first began working with Christopher to undertake studies of *Leishmania* parasites in the sandfly.

In 1991, Jenefer was recruited to the Glaxo Chair of Molecular Parasitology at the University of Cambridge and went on to become the Founding Director of the new Cambridge Institute for Medical Research. Christopher was

lured to Cambridge to head up a field project in Brazil to study genetic susceptibility to tuberculosis, leprosy and leishmaniasis. He studied leishmaniasis families for his PhD research, while Sarra was recruited as a student to study tuberculosis and leprosy families. Both continued in postdoctoral research in the Blackwell lab, and over the succeeding years the team established numerous international research projects on these infectious diseases that still include projects running in Brazil, pan-Europe, Hong Kong, India, Sudan, USA and Vietnam. Richard has played a major role in developing databases and providing bioinformatics support to underpin this human genetics research.

Today, Jenefer retains a position at the Cambridge Institute of Medical Research as an Honorary Senior Scientist and Affiliated Principal Investigator, to continue work on the analysis of DNA from 2000 Indian and 3000 Brazilian individuals in the visceral leishmaniasis study. This position has the added bonus of allowing Jenefer regular visits to the UK to see her children and grandchild.

At the Telethon Institute, major new projects have been initiated by Jenefer and her team including a study of otitis media in Western Australian children, which is cross-cultural and includes Indigenous and non-Indigenous family-based sampling.

"As part of this study, we are working in partnership with the Ngangganawili Aboriginal Medical Service in Wiluna and the Karalundi School in Meekatharra to map complex diseases onto the family trees of the major lineages of Indigenous people in this region of WA," says Jenefer.

"Building capacity in Indigenous populations that will allow Indigenous researchers to play a major role in the research is an important aim of this study."

A particular interest in studying Indigenous and non-Indigenous populations is the interplay between different



above: Professor Jenefer Blackwell, Dr Christopher Peacock and Dr Sarra Jamieson.

diseases, especially between infectious disease and non-infectious diseases like Type 2 diabetes. This forms the basis to an emerging collaboration with researchers in Thailand, which will use genetics to help to understand why Type 2 diabetes is a major risk factor for bacterial diseases like melioidosis (an infectious disease caused by bacteria found in soil and water) and tuberculosis (an infectious bacterial disease transmitted through the air that mainly affects the lungs). Jenefer says her team also hopes that many new collaborations will develop within the Institute.

"Sarrah has recently linked up with Natasha Nassar in the Division of Population Sciences to assist in her research looking for gene by environment interactions that determine rising rates of hypospadias in Western Australia," says Jenefer.

"We will continue our research initiated in Cambridge looking at toxoplasmosis, and this will form the basis to expanding research on congenital diseases, building on the Institute's strong history of analysis of birth defects."

Overall, the team hopes that understanding genetic risk, and its interaction with environment, will contribute to the development of better therapies for both communicable and non-communicable disease.

Division of Cell Biology

The principal research focus in the Division of Cell Biology is upon the cellular and molecular mechanisms underlying resistance and susceptibility to infections and allergic diseases during childhood, in particular those involved in the pathogenesis of inflammatory diseases in the respiratory tract. Earlier work from the Division has established an important paradigm in paediatric medicine, notably that risk for postnatal development of atopy and asthma and related diseases is determined primarily by maturational factors which control the transition of the immune system from the low activity state which is characteristic of fetal life, to the fully functional state seen in latter childhood. The key to this transition is the maturation of a variety of cytokine driven effector functions which are suppressed in utero in order to protect the placenta from inflammatory damage. These same mechanisms are necessary for resistance to both infections and allergy, and we have shown that the rate at which they mature functionally during the preschool years is a key determinant of risk for allergy, respiratory infection and asthma. Much of the work of the Division is targeted at more detailed definition of these mechanisms, with the aim of development of early intervention strategies to reduce disease susceptibility, ideally to prevent disease onset. This includes a significant component devoted to pediatric vaccinology, as many of the underlying immunological principles in this area relate also to asthma/allergy susceptibility. A complementary stream of research in our Division is aimed at elucidation of the mechanisms that regulate the cell populations responsible for triggering T-lymphocyte activation during the "late phase response" in asthma, which is largely responsible for progression from acute to chronic disease. Earlier work from the Division has identified the principal cellular trigger of this response, airway mucosal Dendritic Cells, and most recently we have shown that their pro-inflammatory functions are in turn controlled locally by T regulatory cells. Our ongoing studies in this area are aimed at development of new therapeutic strategies to dampen the pro-inflammatory functions of these Dendritic Cells in asthmatics.

Aetiology And Pathogenesis Of Atopy And Asthma

[The W.A. Pregnancy Cohort 14 year old asthma study](#)

EM Hollams, M Serralha, D Suriyaarachchi, CE Ladyman, A Sadowska, BJ Holt, FT Parsons, B Zhang and PG Holt in collaboration with PD Sly, Clinical Sciences, TICHR

In 2007 we completed *in vitro* analyses and data collection the 14 year follow-up of the W.A. Pregnancy Cohort, which has been followed intensively since birth. We have collected clinical and laboratory data from 1,380 cohort members, with the aim of elucidating asthma and allergy phenotypes in this age group. These data cover four broad areas: clinical history, genetic profile, lung physiology and immunology of the participants. Immunological assays undertaken have included allergen skin prick testing, haematology, and measurement of IgE and IgG4 to seven different allergens, measurement of eosinophil cationic protein and soluble CD14 from plasma, as well as, eosinophil protein X and prostaglandin F₂α from urine. In addition, we have investigated both allergen-specific T-cell immunity and global measures of innate and adaptive immune competence, and have obtained genotypic information on a large panel of atopy/asthma candidate genes. Statistical analysis and modeling of the data is in progress to identify biomarkers, which predict risk for and/or severity of asthma and related respiratory and allergic conditions. Analyses thus far have uncovered several novel determinants of asthma risk, in addition to validating some known risk factors for asthma and allergy. The long-term objective is integration of the information collected to identify biomarkers, which discriminate asthma subgroups, with the aim of improving diagnosis and treatment in this age group.

This research is funded by the National Health & Medical

Research Council of Australia and the Stanley Trust, UK.

Genome-wide identification of novel genes involved in acute asthma exacerbation in children

LS Subrata, E Mamessier and PG Holt in collaboration with P Le Souef and colleagues, School of Paediatrics and Child Health, UWA

Acute severe asthma requiring hospitalisation can be life threatening, with respiratory viral infection being the major triggering agent leading to the exacerbation. The underlying inflammatory mechanisms responsible for the exacerbation are incompletely understood. We have completed studies on PBMC samples obtained from acute asthma patients and have utilised affymetrix microarray technology to identify novel genes differentially expressed *in vivo* during the acute versus convalescent stages of the disease. Analysis of the microarray data identified a large panel of differentially expressed genes, which belong to several relevant immunological/inflammatory cascades including arachidonic acid/prostaglandin signalling, leukocyte migration, innate immunity, adaptive immunity, complement and coagulation, and inflammation-associated pathways. We selected 54 of the most differentially expressed genes representative of these pathways for PCR validation, and 98% of the genes were successfully validated at the mRNA level. We found that approximately 60% of the genes correlated significantly with the degree of exacerbation severity, and about 20% of the genes were potentially affected in their expression by steroid treatments at the time of hospitalisation. We also performed flow cytometry experiments using available antibodies, and confirmed the differential gene expression at the protein level. We next utilised cell sorting to further investigate the

cellular source of the gene expression observed and documented the differential expression of relevant genes in innate and adaptive cell types. The overall data from the study is still being collated, but it is clear from the analyses to date that the most prominent gene expression signature associated with acute exacerbation is within cells of the innate immune system.

This research is funded by the National Health & Medical Research Council of Australia.

Immunoprophylaxis of asthma and atopy

PG Holt in collaboration with PD Sly, Clinical Sciences, TICHR, R Loh, Princess Margaret Hospital, P Robinson, Royal Children's Hospital, Melbourne, H Sampson, Mount Sinai School of Medicine, New York, B Björkstén, Allergy Centre, Karolinska Institute, Stockholm and U Wahn, Charité - Universitätsmedizin, Berlin

After three years of intensive planning, in July 2006 we initiated a multicentre clinical trial on asthma/allergy prevention in high risk children in Perth, Melbourne and New York, under the auspices of the Immune Tolerance Network (ITN) of the US National Institutes of Health. The trial is testing a radical method for prevention of these diseases in "high risk" children, employing a vaccine-like approach which is conceptually a mirror image of that used for prevention of infectious disease i.e. stimulation of development of immunological tolerance as opposed to active immunity. This trial strategy is based on the results of research in TICHR and in other centres in Europe and USA, indicating that the basis for natural resistance to sensitisation to inhalant allergens, and hence resistance to atopic asthma, is the development during early childhood of a form of immunological tolerance to inhaled allergen.

This process is driven by repeated allergen exposure of the mucosal surfaces of the oropharynx, the nose, and the large airways, and the overall efficiency of tolerance induction is directly related to exposure intensity. In the trial we are seeking to increase the efficiency of the tolerance process in children at risk of allergy, by repeated exposure of the oral mucosa over for a one year period to a mixture of the three most important aeroallergens known to be associated with asthma in the areas of the trial centres in Australia, USA, Sweden and Germany (notably house dust mite, cat and grass allergens). The aim of this initial trial is to reduce atopy and asthma prevalence in these children over a 3 year follow-up period by 50%. An important component of the trial design involves detailed investigations on underlying allergen-specific immune responses in the children throughout the study period, to provide definitive information on underlying mechanisms. In response to requests from the US Food and Drug Administration who set the safety parameters for the trial, we have now taken an initial group of 50 children through the first 6 months of treatment in Australia and the US and have established safety, prior to opening up the additional trial sites in Europe to recruit a further 150 subjects. At the time of writing this report the results of the 6 month assessment are being reviewed by ITN to seek interim proof of efficacy, based on the demonstration of treatment-induced changes in IgE and/or IgG4 antibody levels. The results of the assessment will determine whether the trial funding continues beyond this first group of 50 children.

This research is funded by the US National Institutes of Health Immune Tolerance Network.

Effects of severe respiratory syncytial virus (RSV) infection on development of immune functions during infancy

E Mamessier, LS Subrata and PG Holt in collaboration with PD Sly, Clinical Sciences, TICHR

Respiratory syncytial virus (RSV) is a major cause of severe low respiratory infection in infants and young children, leading to diseases such as pneumonia and bronchiolitis. Young children with severe RSV infection have an increased risk of developing childhood asthma later in life. We have completed studies on early immune development in two groups of RSV infected infants with mild versus severe bronchiolitis. PBMC samples were collected at ten days post-hospitalisation (Visit 1) from infants within the 2-6 months age range, then three months later (Visit 2), and finally at the age of 18 months (Visit 3). In response to *in vitro* RSV stimulation, PBMC from the severe bronchiolitis group produced high levels of IFN γ , IL10, IL5, IL13, TNF and IL6 cytokines, in contrast to the mild bronchiolitis group which produced little or none of the cytokines, except for IL6. We also observed that IFN γ and IL10 production in the severe group increased over time (Visit 1 to 3), whereas IL5, IL13, TNF and IL6 decreased over time. Investigation of the cellular source of the cytokine production showed that both T and non-T cells contributed to the *in vitro* RSV response. Additionally, we observed a higher proportion of CD8⁺ T cells in the severe than the mild group. We further investigated by flow cytometry the expression of TLR4, which is one of the major toll-like receptors implicated in RSV clearance. Mean fluorescence intensity of TLR4 expression on monocytes was significantly increased in response to the TLR4 agonist LPS in the mild group, while no response was observed in the severe group, suggesting the inability of the severe group to upregulate TLR4 expression for RSV clearance. In response to the T cell mitogen PHA, we found increasing IFN γ production

over time (Visit 1 to 3) in the severe but not mild group, and decreasing IL10 production over time in the mild but not severe group. This suggests a more sustained inflammation in the severe compared to the mild group, at least 18 months post infection. In line with this, a similar trend was observed in a high risk childhood asthma cohort. Increasing IFN γ production was similarly observed over time (6 vs. 12 months old) in RSV-infected but not non-infected children, and decreasing IL10 production was observed in non-infected but not RSV-infected children. Together, this study has demonstrated that the severity of primary RSV infection in infants has significant effects on early immune development. More severe primary RSV infection is likely to lead to a prolonged immune response, mainly consisting of cytotoxic Th1 and inflammatory responses, with TLR4 playing an important role.

This research is funded by the National Health & Medical Research Council of Australia.

Innate Immunity

Airway epithelial cells and regulation of dendritic cell function

A Rate, JW Upham and PG Holt

Dendritic cells (DC) are the major antigen presenting cells of the lung and are closely regulated by signals in their microenvironment. DC and their precursors are in intimate association with airway epithelial cells (AEC) and recent published data suggests that AEC can influence DC differentiation and maturation. This study aims to further characterise and elucidate the mechanisms behind AEC regulation of DC maturation. We have developed an *in vitro* AEC line/monocyte co-culture system, whereby in the presence of IL-4 and GM-CSF, maturation of monocytes

into DC can be monitored. At Day 5, DC differentiated in the presence of AEC retain CD14 expression yet express higher levels of MHC and co-stimulatory molecules compared to control DC. In addition, these cells are adept at sampling and processing antigen, functions generally ascribed to their more immature precursors. Antigen presentation to T-cells by the AEC-conditioned DC reveals a bias away from a Th2 response which is the dominant form of Th-immunity when atopic T-cells are co-cultured with control DC. In view of these results, we used microarray technology to compare the gene expression profiles of the individual DC populations generated with or without AEC. Preliminary results have revealed that AEC conditioning results in a strong type I interferon signature in maturing DC that may represent an important component of the mechanism of this DC modulation. Currently, functional studies are underway to validate the role of type I interferon in this AEC-DC cross-talk. Furthermore, investigations are continuing into the mechanisms behind the downstream modulation of T-cell responses by the AEC-conditioned DC.

This research is funded by the National Health & Medical Research Council of Australia.

Pre-symptomatic differences in toll-like receptor function in infants who develop allergy

MK Tulic in collaboration with SL Prescott, P Noakes, B Chow, L Breckler, School of Paediatrics and Child Health, UWA, and in collaboration with CA Thornton, School of Medicine, University of Swansea, UK

This study explored the hypothesis that impaired function of Toll-like receptor (TLR) microbial recognition is a key factor in allergy development. Cord blood mononuclear cells samples were cultured either alone or with optimal

concentrations of TLR ligands: lipoteichoic acid (TLR2), polyinosinicpolycytidylic acid (TLR3) lipopolysaccharide with interferon gamma (IFN- γ) (TLR4), flagellin (TLR5), Imiquimod R837 (TLR7) and CpG (TLR9). Supernatants were analyzed for cytokine responses. Questionnaires, clinical assessment and skin prick testing were used to assess allergy risk (maternal allergy) and allergy outcomes (food allergy and atopic dermatitis) at 12 months of age. Maternal allergy was associated with significantly *higher* neonatal responses (particularly IL-12 and IFN γ) to TLR2, TLR3 and TLR4 activation. Consistent with previous reports, neonates who subsequently developed allergic disease had *lower* Th1 IFN γ response to mitogens (phytohaemagglutinin). However, these infants had significantly *higher* TLR mediated responses than those without subsequent disease (n=75), notably inflammatory TNF α ; and IL-6 responses to TLR2, TLR2, TLR4 and TLR5 activation. The presence of pets in the maternal household was associated with significantly higher neonatal IFN γ responses to all TLR ligands tested (TLR2, 3, 4, 5, 7, 9). We concluded that allergic disease was associated with increased (rather than decreased) perinatal TLR responses. Further studies are needed to determine how these responses track in the postnatal period and if this relative hyper-responsiveness is a product of intrauterine influences, including maternal atopy and/or functional genetic polymorphisms.

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

Ido-positive eosinophils in thymuses of young children: potential role in maturation of the naïve immune system

MK Tulic, PG Holt in collaboration with PD Sly, Clinical Sciences, TICHR, and in collaboration with D Andrews, M Crook and A Charles, Divisions of Cardiac Surgery and Paediatric Pathology, PathWest Laboratory Medicine, Princess Margaret Hospital, Perth, Australia, and in collaboration with F Davoine, SO Odemuyiwa, O Surname and R Moqbel, Pulmonary Research Group, University of Alberta, Edmonton, Canada

Babies are born with relatively immature immune systems, which is Th2-skewed at birth. The thymus is thought to play an important role in maturation of the adaptive immune system during early childhood with both the size and its importance diminishing in later life. Currently little is known about how the thymus instructs immune maturation after birth in humans. Recent data from mice suggests that cells from the innate immune system, in particular eosinophils that reside within the thymus, may be involved in this education process. We hypothesized that eosinophils are present in thymuses of children and may thus participate in early events leading to Th2 skewing. Moreover, an eosinophil-derived intracellular enzyme idoleamine 2, 3-dioxygenase (IDO), which is involved in catabolism of an essential amino acid tryptophan, may play an important role in promoting early Th2 polarization. To test this hypothesis, we collected thymuses from children (7 days to 12 years) undergoing open-heart surgery and tissue was processed for histological as well as molecular analysis. In addition, supernatant from homogenized tissue was used to measure baseline cytokine/chemokine protein levels. Luna-positive eosinophils were detected in thymuses of children and their number decreased with age.

Eosinophils were not only present in the trabeculii but also in the medullary region of the thymus as well as inside the Hassle's corpuscles. FACS analysis showed eosinophils to represent ~2% of the total thymic cell population. High expression of IDO mRNA was detected in the thymus and the majority of eosinophils were IDO-positive. In addition, we detected high mRNA expression of Th2 (GATA-3, STAT-6, IL-4, PGE2 receptor) and regulatory (Foxp3, IL-10) genes, as well as innate receptors (TLR-2, -4, -7, -9, MD-2); expression of the latter markers steadily increased temporally up to age 5. However, the level of constitutive IL-5 and IL-13 protein in the supernatant was greatest in the youngest children and this was correlated with their eosinophil numbers in the thymus (r=0.44).

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

Vaccine Studies

Vaccine-specific Th2 memory responses are associated with large local reactions following pre-school vaccination with diphtheria, tetanus, acellular pertussis

J Rowe, O White and PG Holt in collaboration with P Richmond, School of Paediatrics and Child Health, UWA

We have recently demonstrated a potential link between the type of cell-mediated memory response generated in infancy following vaccination with the diphtheria tetanus acellular pertussis vaccine (DTaP; vaccine given at 2, 4, 6 and 18 months) and the incidence of large local reactions following administration of the pre-school DTaP booster. Immunological studies on these children indicate that local reactions are associated with pre-existing and

boostable T-helper 2 (Th2)-polarised immunological memory to vaccine antigens demonstrable in both the humoral (IgE) and cellular immune (IL-5, IL-6 and IL13) compartments. Recently, the Standard Australian Vaccination Schedule has changed with respect to DTaP, with the removal of the 18-month dose. We aim to determine what effects removal of this DTaP dose has on the persistence of vaccine-specific memory and the incidence of local reactions seen following the pre-school dose. Currently, 70 out of the anticipated 100 pre-school aged children have been recruited into the study, and blood samples collected at the time of DTaP administration, and again 6 weeks later. Vaccine-specific humoral and cell-mediated immunity are being examined as per the forerunner study. In addition, we will use micro-array technology to gain further insights into the Th2 pathway of immune memory and the inflammation associated with the large local reactions.

This research is funded by the National Health & Medical Council of Australia.

Neonatal immunization with pneumococcal conjugate vaccine in Papua New Guinea

AHJ van den Biggelaar, MA Nadal-Sims, C Devitt and PG Holt in collaboration with D Lehmann, Population Sciences, TICHR, and in collaboration with P Richmond, School of Paediatrics and Child Health, UWA, and in collaboration with S Phuanukoonnon, W Pomat, and P Siba, Papua New Guinea Institute of Medical Research

Infants in Papua New Guinea (PNG) are at high risk for neonatal onset of dense respiratory tract pneumococcal (Pnc) colonisation (median age of colonization is 17 days), which is associated with increased risk of invasive pneumococcal disease. In order to protect these

high-risk groups from early Pnc disease and mortality, neonatal immunization with pneumococcal conjugate vaccine (PCV) has to be considered. Our current study in the PNG highlands is aimed at showing the safety and immunological feasibility for such a vaccination strategy. The trial involves 319 newborns that have been randomised to receive PCV either at 1) birth-1mo-2mo, or 2) 1mo-2mo-3mo or 3) receive only routine immunizations (control group). Venous blood samples to determine cellular and/or humoral immune responses to the vaccine and bystander antigens are collected at birth, and at 2, 3, 4, 9, 10 and 18 months of age. In addition, bacterial carriage is assessed weekly for the first month of life and at regular intervals thereafter. Children are followed for respiratory and other diseases throughout the study. In 2007, all children had completed their 3 month follow up (first time point of venous blood collection for cellular immunology) and half of the cohort had completed the full 18-month follow-up period. Sufficient cells were available from 198 children to measure cellular immune responses at 3 months. At this time point, children in the two arms of study vaccine groups produced significantly higher T helper 1 (IFN- γ) and T helper 2 (IL-5 and IL-13) to the vaccine protein carrier CRM₁₉₇ than children in the control group. T helper cell responses to bystander antigens (for example Tetanus toxoid and Hepatitis B soluble antigen) and mitogens (PHA) were similar between the three groups. These first data demonstrate that the study vaccine induces memory T cell responses in PNG children even when given at birth, with no spill-over effect on bystander antigens. Together with the finding that the frequency of systemic and local side effects 48 to 96 hours after vaccination with PCV was very low, these first immunological outcomes indicate that neonatal and infant immunization with PCV is safe and immunogenic in PNG.

This research is an International Collaborative Research Grant funded by the Wellcome Trust, UK and the National Health & Medical Research Council of Australia.

Immuno-epidemiology of Bacille Calmette-Guérin (BCG) vaccination

AHJ van den Biggelaar and PG Holt in collaboration with SL Prescott, School of Paediatrics and Child Health, UWA, and in collaboration with P Siba, Papua New Guinea Institute of Medical Research

Infants in low-income countries are vaccinated with BCG, preferably within the first month of life. BCG vaccination induces protective T helper 1-memory responses in this young age group, but its efficacy appears to vary within and between populations. The immunology that may underlie this variation has never been studied. One approach to address this problem is elucidation of the potential pro inflammatory effects of BCG on innate immune responses of newborns in low versus high infection environments, typified by the PNG: Perth populations described above. Our data from these comparisons show that in PNG newborns innate immune responses to BCG were skewed towards the typical polarized neonatal response, as defined by significantly higher IL-6 and IL-10 responses. IFN- γ priming enhanced BCG-induced IFN- γ , TNF- α , IL-12 and type-I interferon responses in both groups, but to a significantly higher extent in Perth newborns. This was most apparent for the IFN- γ , which was boosted 150-fold in Perth newborns but only 8-fold in PNG newborns. These differences in responsiveness to IFN- γ were reflected in relative expression levels of IFN γ R1 and IFN γ R2. In Perth newborns, but not PNG newborns, NK-cells were a principal source of BCG-induced IFN- γ production. These findings imply that in high infectious environments BCG-

induced innate immune responses are skewed towards negative immune regulation, which may increase the threshold to induce protective immune responses and hence limit vaccine efficacy. In our second approach we aim to address this longitudinal association between innate immune responses to BCG and subsequent development of protective T helper 1 responses during the first 18 months. In this prospective birth cohort study we will also examine the potential spill-over effect of BCG on other childhood vaccines and immune ontogeny in general, while taking into account the age and hence relative order in which BCG is given in relation to other childhood vaccinations.

This research is funded by an International Collaborative Research Grant from the Wellcome Trust, UK, the National Health & Medical Research Council of Australia, and an UWA Research Grant.

Meningococcal B vaccine trial

J Rowe, O White, M Serralha and PG Holt in collaboration with P Richmond, School of Paediatrics and Child Health, UWA

Meningococcal disease occurs most often in young children and teenagers. It is caused by the bacteria *Neisseria meningitidis*, which is an obligate human pathogen carried in the upper respiratory tract by around 5 - 10% of the population. On occasions, the bacteria disseminate to cause invasive disease such as bacteremia and meningitis. Early antibiotic treatment is often successful, although prevention through vaccination is the ultimate goal. Currently, the only vaccine available is to *N. meningitidis* serotype C (polysaccharide conjugate vaccine), although 50 -70% of disease in developed countries is caused by serotype B.

However, vaccine development for meningococcal B has been difficult as the polysaccharide capsule is poorly immunogenic in humans and has structural similarities to human neural antigens, raising questions of safety. Consequently, Wyeth has developed a candidate meningococcal B vaccine (vaccine is based on a surface exposed lipoprotein) that is currently in Phase I clinical trials. As part of this trial, healthy adults have been given 3 doses of the candidate meningococcal B vaccine (at 0, 1 and 6 months), and we have cryobanked blood samples before and after each dose. We have now concluded the clinical phase of this study and have optimised the *in vitro* culture system. Currently, we are in the process of utilizing the cryobanked blood samples to examine the generation of cell-mediated immunity to the lipoprotein contained in the meningococcal B vaccine. This data will be merged with data on humoral immunity obtained by Wyeth in order to obtain a complete understanding of what effect this vaccine is having on immune function.

This research is funded by Wyeth Pharmaceuticals.

Immune ontogeny in infants in the developing and developed world

AHJ van den Biggelaar and PG Holt in collaboration with SL Prescott and P Richmond, School of Paediatrics and Child Health, UWA, and in collaboration with D Stanicic and S Phuanukoonnon, Papua New Guinea Institute of Medical Research

Microbial exposure in early life is postulated to drive the maturation of the neonatal immune system from predominantly T helper 2 (Th2) to protective T helper 1 (Th1) responses. Although this pattern of immune development has been well described for children in

developed countries, it is not known whether these mechanisms hold true for children in the developing world where higher exposure to infectious pathogens has been associated with activation of immune regulatory mechanisms. In order to test the general applicability of this paradigm, we are directly comparing immune responses in cord blood mononuclear cells obtained from births in Papua New Guinea (PNG), with those from newborns in the metropolitan area of Western Australia, and again in peripheral blood mononuclear cells when the children are one year old. Our main focus is on the Toll-like receptor (TLR) system and the regulatory T cells, and their relationships to early T cell development. Detailed information on malarial and helminth infections during pregnancy and indoor air pollution are collected to study their direct or indirect (via low birth weight and low gestation age) impact on *in utero* and postnatal immune modulation. This study will provide timely data on neonatal immunological pathways that are central to resistance to infectious diseases and vaccine efficacy in Third World paediatric populations who are at greatest risk of infectious diseases. In particular, it may provide insight into the choice of vaccine adjuvant strategies, which are most relevant to Third World settings.

This research is funded by the National Health & Medical Research Council of Australia and an UWA Research Grant.

Vaccination at birth for the prevention of whooping cough (pertussis)

J Rowe, O White and PG Holt in collaboration with Peter McIntyre and Nicholas Wood, National Centre For Immunisation Research and Surveillance, University of Sydney, NSW

Whooping cough (pertussis) is a disease that can affect all age groups, although it is the very young (less than 6 months of age) who are at most risk of severe disease. In children, pertussis vaccines are given at 2- 4- and 6-months of age, but until the 3-dose primary vaccination regime is complete, children are still at risk. One potential strategy to induce earlier protection against pertussis infection would be to vaccinate children at birth, with the aim of inducing a protective immune response in the first crucial months of life. In a collaborative study with the National Centre for Immunisation Research and Surveillance, we examined the level of protection achieved in a cohort of 50 children following the standard vaccine schedule (vaccine administered at 2-, 4- and 6-months of age) either alone, or together with an additional vaccine dose given at birth. Blood was collected at birth, and at 2, 4, 6 and 8 months of age. Our data provide evidence that neonatal pertussis vaccination induces significantly higher levels of vaccine-specific IgG antibody as early as 2 months of age compared to those vaccinated according to the current schedule. At 8 months of age, the levels of vaccine-specific IgG were similar in all 3 groups, but those given pertussis vaccination at birth displayed vaccine-specific cell-mediated immunity that was strongly skewed towards production of Th2 cytokines. In order to determine the persistence of immunity to pertussis, blood is currently being collected from these children at 2 years of age.

This research is funded by the National Health & Medical

Research Council of Australia.

Animal Model Studies

Airway mucosal DC (AMDC) maturation is controlled by local T cell interaction following repeated antigen challenge

DH Strickland, JA Thomas, S Judd, M Wikstrom and PG Holt in collaboration with A Larcombe, DJ Turner and PD Sly, Clinical Sciences, TICHR, and in collaboration with FL Jahnsen, Department of Pathology, Rikshospitalet, Oslo

Our studies have shown that activation of AMDC within the respiratory mucosa, following aerosol challenge of sensitised animals, is central to the development of the Th2 driven rat equivalent allergic asthmatic response. The asthma late phase response and ensuing development of airways hyper-responsiveness (AHR) occurs as a result of subsequent airway mucosal T cell activation. Results from our rat model studies show that continuous antigen exposure facilitates the development of T regulatory cell (T reg) compartments within respiratory tissues, which can be adoptively transferred into sensitised animals and act to inhibit the development of AHR following aerosol challenge, providing an "off switch" during asthma exacerbations. Thus, our results indicate that the functions of AMDC and T reg cells are linked with the development and subsequent regulation of airway mucosal T cell activation. These initial studies have utilised the PVG rat strain, typically a low IgE responder, to evaluate immunological aspects of the asthmatic response. More recent studies have focused on characterising this allergic airways inflammatory disease in the BN rat, a high IgE responder that more closely exemplifies an allergic status. Results from this study have indicated major differences between high and low IgE responder strains on the basis of both DC and T reg components of the response of

sensitised animals to aerosol challenge. In particular, there are apparent differences in baseline phenotypes and localisation within tissues at the level of DC and T cell compartments. Differences also exist in relation to these cellular types in the responses observed following a single and multiple aerosol challenges. Additionally, T reg recirculation is implicated as playing a possible role in the inability of the BN rat to re-establish homeostasis within the airways following continuous antigen exposure. To gain a better understanding of the role of DC, Th2 and T reg compartments within respiratory tract tissues and their possible interactions, we have been characterising DC subsets, with particular emphasis on evaluating phenotypes, antigen transport from airways to draining lymph nodes, activation, and functional capacity of different subsets, during both normal homeostasis and following sensitisation and challenge. To complement these studies, confocal microscopy tools are being utilised to localise and visualise antigen uptake within the respiratory mucosa. These tools are also being utilised to visualise DC and T reg interactions within airway respiratory tract tissues. The functional capacity of T reg cells, which develop in response to antigen exposure, is being characterised in these different rat strains. Highly purified populations of DC subsets, with characterised roles, and T reg cells from both normal animals and animals following sensitisation and various aerosol challenge regimens are being collected for genome expression profiling.

This research is funded by the National Health & Medical Research Council of Australia.

Identification of a candidate progenitor cell for dendritic cells and other antigen presenting cells (APC) within the mouse respiratory tract

DH Strickland, M Wikstrom, C vonGarnier, PG Holt and PA Stumbles

It remains unclear at present if RT-APC are derived from resident pluripotential progenitors or if differentiated early precursors are recruited from the blood to maintain APC populations within RT tissue. We have previously identified a novel population of cells confined to the lung parenchyma with rapid turn over kinetics and DC/monocyte characteristics, at the phenotype and morphological levels. These cells have the capacity to differentiate *in vitro* into DC and macrophage populations following exposure to GM-CSF. Work this year has been focused on further phenotypic and functional characterisation of this precursor population. The aim of the study is to be able to sort these cells to high purity, tag the cells (to enable later identification) and track their fate following adoptive transfer.

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

Effects of feeding microbial derived immunostimulants (MDI) on aspects of allergic airways inflammation

DH Strickland, S Judd, JA Thomas, PG Holt in collaboration with A Larcombe, DJ Turner and PD Sly, Clinical Sciences, TICHR, and in collaboration with OM Pharma, Switzerland

In collaboration with OM Pharma, we have been studying the effect of feeding MDI to animals, following sensitisation, on the subsequent development of

allergic airways inflammation in our rat allergic asthma model. Oral administration of these agents to humans has been associated with protective effects against the development of diseases such as bronchitis. The emphasis of this study has been to determine if feeding of MDI to sensitised animals prior to aerosol challenge can modify responses at distal sites within respiratory tract tissues that are commonly associated with this disease model. Of particular interest are responses at the level of DC activation, T reg compartments and Th2 responses. The key findings from this study to date demonstrate that feeding MDI to sensitised animals prior to aerosol challenge results in a significant reduction in airways inflammation, which is also accompanied by a significant increase in the numbers of T reg cells, particularly within the airway mucosa. Additionally, these effects were translated into a significant reduction in the development of airways hyperresponsiveness at the peak of the response.

This research is funded by OM Pharma, Geneva, Switzerland.

Cellular and molecular pathways regulating airway mucosal dendritic cells (AMDC) during onset of allergic airways inflammation (AAI)

P Stumbles, M Wikstrom, D Strickland, K Wijkvist, S Judd, V Fear, P Holt in collaboration with D Turner, P Sly, J Burchell and G Zosky, Division of Clinical Sciences, TICHR, and in collaboration with C von Garnier, Berne, Switzerland

These studies are part of an on-going project NHMRC grant to examine the following aims: (1) *How is airborne allergen uptake and processing by subsets of AMDC regulated within the mucosa of the large conducting*

airways during development of AAI? These studies showed that AMDC function is dysregulated during the onset of allergic airways disease, supporting our first hypothesis that upregulation of AMDC processing and presenting function is a prelude to the onset of AAI. We also showed that allergen-specific antibody plays an important role, either through opsonisation of allergen and/or through direct FcR signaling effects on AMDC that upregulate AMDC antigen processing and presentation, and in promoting CD4⁺ T cell proliferation within the airways of mice exposed to inhaled allergen. To test this hypothesis, FcR common gamma chain knock out mice are currently being rederived and should be on-line by mid 2008. We plan to investigate the role of FcR signaling in promoting AMDC allergen processing capacity, as well as investigate the relative contributive roles of allergen-specific IgG and IgE. (2) *What interactions occur between AMDC and CD4⁺ T cells in DLN and what is the longevity of this response?* We have been actively investigating this aspect of the project, and have employed a variation of the standard acute disease model whereby mice are exposed for an extended period of time (up to 16 allergen exposures over a period of 4 weeks) in order to investigate the longevity of the upregulated AMDC antigen processing activity and the ensuing nature of the allergen-specific T cell response, both in DLN and airways. In contrast to the acute exposure regime, AMDC activity is down-regulated after prolonged exposure and this correlates with significantly reduced physiological measures of airways hyperresponsiveness (AHR), allergen-specific T cell proliferation in the DLN and the appearance of elevated numbers of CD25⁺ FoxP3⁺ regulatory T cells in the DLN and airways. Importantly, we have also shown that suppression of AHR and T cell proliferation can be adoptively transferred to acute-phase mice using T regulatory cells isolated from mice

undergoing prolonged allergen exposures and we are currently further investigating the molecular mechanisms involved (3) *What are the conditions regulating generation of effector populations of lung-homing Th2 cells and what is the potential for local tissue selection of pro-allergic Th2 cells?* Work has commenced in this area, initially through use of the DO11.10 TCR transgenic mouse strain in which mice were exposed intranasally to allergen and T cells harvested from DLN and airways at various time points after allergen exposure. We have made use of commercially available PCR arrays for the analysis of mRNA expression for a variety of chemokine and chemokine receptor genes involved in T cell trafficking. This has yielded a large amount of data that we are in the process of analysing and confirming by protein expression. Of particular interest from our point of view is that there appears to be differential usage of chemokine receptors by T cells depending on whether they home to the airway mucosa or lung parenchyma and also differential chemokine receptor usage by naive, recently activated and memory T cells in the airways.

This study is funded by the National Health & Medical Research Council of Australia.

Mechanisms mediating CD4⁺ T cell homing to the respiratory tract

ME Wikstrom, K Wqvist, PG Holt, PA Stumbles

CD4⁺ T cells are crucial players in the immune response of the respiratory tract. When an allergen is inhaled, a cascade of events takes place leading to the activation of CD4⁺ T cells in the draining lymph nodes. A proportion of these activated cells appears to be programmed to migrate out of the lymph nodes and travel (or home) to the respiratory tract where they can direct the local

immune response. The purpose of this project is to learn more about the mechanisms responsible for CD4⁺ T cell homing to the respiratory tract. To this end, activated T cells were collected from lung tissue so that their RNA could be extracted for gene expression analysis. Several genes for chemokine receptors were upregulated in lung CD4⁺ T cells including CCR4, CCR5, and CCR8. These molecules have previously been shown to be important for guiding T cells to the respiratory tract. However, when single cells were analysed by flow cytometry, only a small proportion actually expressed these receptors on their cell surface. One possible explanation for this unexpected result is that CCR4 and CCR8 are lost from the cell surface soon after the T cells arrive in the respiratory tract. Over the next twelve months we will be looking more closely at this issue by measuring chemokine receptor expression on T cells before they enter the respiratory tract. We will also start work on identifying the cell types responsible for inducing the expression of CCR4 and CCR8.

This research is funded by the National Health & Medical Research Council of Australia.

Staff and Students

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Dr Marjut Roponen PhD, Department of Environmental Health, National Public Health Institute, Kuopio, Finland.

Research Support

Anne Amourgis

Theses passed

Anthony Bosco PhD University of Western Australia: Identification of novel genes associated with allergen-

driven T cell activation in human atopics.

Angela Taylor PhD University of Western Australia: Allergy Prevention Studies: The role of probiotics in allergy prevention in high-risk infants.

External Committees

International

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

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

National

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.

John Upham. National Health & Medical Research Council of Australia Training Award Committee.

John Upham. National Health & Medical Research Council of Australia, Grant Review Panel.

John Upham. Asthma Foundations of Australia, Medical & Scientific Advisory Committee.

John Upham. Education and Research Subcommittee, Thoracic Society of Australia & New Zealand.

Invited Presentations

Patrick Holt. Immunologic susceptibility towards allergy in the newborn (The Charles Reed Memorial Lecture). American Academy of Allergy, Asthma & Immunology, San Diego, 2007.

Patrick Holt. Modulation of IgE mediated diseases in children. World Allergy Forum Symposium, XXVI Congress of the European Academy of Allergy & Clinical Immunology, Gothenburg, 2007.

Patrick Holt. New findings from birth cohort studies. World Allergy Forum Symposium, XXVI Congress of the European Academy of Allergy & Clinical Immunology, Gothenburg, 2007.

Patrick Holt. Immunophenotyping of allergic disease and tolerance. World Allergy Forum Symposium, XXVI Congress of the European Academy of Allergy & Clinical Immunology, Gothenburg, 2007.

Patrick Holt. Immunoprophylaxis of allergy. International workshop on Future of Allergy Vaccines, GlaxoSmithKline, London, 2007.

Patrick Holt. Viral infection and asthma. Aspen Allergy Conference, Colorado Allergy Society, Aspen, 2007.

Patrick Holt. Making Health Research Relevant: A Multidisciplinary Approach to Asthma Prevention. Division of Health Sciences, University of Otago, Dunedin, 2007.

Patrick Holt. Development of mucosal tolerance to non-pathogenic protein antigens. EAACI/ERS Pediatrics Joint Meeting, Lisbon, 2007.

Patrick Holt. Determinants of susceptibility to atopic asthma in early life. German Inter-Regional Collaborative Research Centre meeting "Allergic Immune Responses in the Lung", Marburg, 2007.

Patrick Holt. Novel strategies to prevent development of allergy. AAAAI Symposium, World Allergy Congress, Bangkok, 2007.

Patrick Holt. Regulation of T cell activation in the airway mucosa. World Allergy Congress, Bangkok, 2007.

Patrick Holt. Novel Th2 associated genes in atopic responses to allergens. ASCIA Symposium, World Allergy Congress, Bangkok, 2007.

Phil Stumbles. Airway dendritic cell function in allergic airways disease. Department of Medicine, Berne University Hospital, Berne, September 2007.

Elysia Hollams. Immunoepidemiology of asthma and allergic disease in a large cohort of 14 year-olds. 2007 Annual Meeting of the Australasian Society for Immunology, Sydney, December 2007.

Angela Rate. Maintaining the balance: epithelial cell – dendritic cell cross-talk in the

lung. UWA Combined Biological Sciences Meeting, Perth, August 2007.

Angela Rate. Maintaining the balance: epithelial cell – dendritic cell cross-talk in the lung. Australasian Society of Immunology (ASI) Annual Conference, Sydney, December 2007.

Angela Rate. Airway epithelial cells suppress *in vitro* monocyte-derived dendritic cell

differentiation and maturation in a co-culture system. European Respiratory Society (ERS) Annual Conference, Stockholm, September 2007.

Julie Rowe. Pre- versus post-natal sensitisation in a high risk cohort. Australasian Society for Immunology, 37th Annual Scientific Meeting, Sydney, December 2007.

Deborah Strickland. Interactions of Dendritic cells, Th2 cells and T regulatory cells in the regulation of homeostasis within the airway mucosa. World Immune Regulation Meeting, Davos, April 2007.

Meri Tulic. Toll-Like Receptor (TLR)-4 Polymorphisms Mediate Impaired Responses to Respiratory Syncytial Virus (RSV) and Lipopolysaccharide (LPS). World Asthma Meeting, Istanbul, June 2007.

Anita van den Biggelaar. Genetic variation in interleukin-10 predicts atopic reactivity in Gabonese schoolchildren. Australasian Society for Immunology, 37th Annual Scientific Meeting, Sydney, December 2007.

Anita van den Biggelaar. Innate immunity in Papua New Guinean and Australian newborns: implications for neonatal (BCG) vaccination?. Australasian Society for Immunology, 37th Annual Scientific Meeting, Sydney, December 2007.

Anita van den Biggelaar. Innate immunity in Papua New Guinean and Australian newborns: implications for neonatal (BCG) vaccination?. 5th World Congress of the World Society for Pediatric Infectious Disease, Bangkok, November 2007.

Anita van den Biggelaar. Neonatal immunization with pneumococcal conjugate vaccine in Papua New Guinea. Wellcome Trust Asia-Pacific Networking Workshop, Beijing, October 2007.

Anita van den Biggelaar. Genetic variation in Interleukine-10 predicts atopic reactivity in Gabonese schoolchildren. Genomics of Common Diseases, Wellcome Trust Centre, Cambridge, July 2007.

Division of Children's Leukaemia & Cancer Research

Paediatric cancers comprise a spectrum of diseases. More than half of them affect cells of the immune system and the central nervous system, while only a minority involve epithelial cells, contrasting with cancers in adults. Thus, 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 are both members of the largest study group into these diseases, the US-based Children's Oncology Group (COG).

The research program of the division focuses on childhood leukaemia and brain tumours. 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. The initial studies involved our panel of established leukaemia cell lines since they are ideal tools for subsequent testing of potential new drugs for the treatment of patients. Currently, a large study on primary patient specimens is in progress with the ultimate aim to achieve improved risk stratification for acute lymphoblastic leukaemia (ALL) patients and to understand the genetic basis for chemoresistance.

Acute lymphoblastic leukaemia

Prediction of relapse in paediatric acute lymphoblastic leukaemia (ALL) using gene risk index

K Hoffmann, JR Freitas, AH Beesley, AL Sherwood, NC Sturges and UR Kees in collaboration with MJ Firth, KU Perera and NH de Klerk, Division of Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research and DL Baker, Department of Haematology-Oncology, Princess Margaret Hospital, Perth, Western Australia.

Despite the high cure rates, resistant forms of childhood ALL constitute a leading cause of cancer-related morbidity and mortality in children. The clinical outcome measured as 5 year event-free survival (EFS) has reached up to 85% for patients classified as standard risk (SR) and 64-75% for high risk (HR) patients. However, a substantial number of patients currently classified and treated as SR patients continue to relapse, highlighting an urgent need for a more comprehensive risk stratification at the time of diagnosis. We examined the use of gene expression profiles (GEPs) to predict long-term clinical outcome in children with ALL. We initially analysed GEPs from 55 pre-B ALL patients using HG-U133A arrays. Subsequently, a multigene classifier for outcome prediction was developed and confirmed by quantitative RT-PCR (qRT-PCR). Supervised outcome-prediction analysis identified 18 genes that predicted outcome with a high accuracy of 89%. This 18-gene classifier was not only significantly linked to clinical outcome, but was also more predictive of outcome than conventional parameters currently used for risk stratification. After feature selection and validation of expression levels by qRT-PCR, a three-gene qRT-PCR risk index was developed based exclusively on data from the array cohort. This index predicted outcome in the array cohort with an accuracy of 89% and in an independent validation cohort (n=46) with an accuracy of 87%. This data demonstrated the feasibility of using GEP to improve stratification in childhood ALL. This is particularly important for the identification of patients

currently stratified as SR for whom more intensive up-front treatments are already available.

We are currently applying the same methodology to study a cohort of 50 T-cell ALL (T-ALL) patients who were all treated on the same COG therapy protocol. The GEPs for these specimens were generated using the most recent and comprehensive HG-U133 Plus 2.0 microarrays (54,657 probe sets). We were able to identify a multigene classifier for prediction of outcome and from this we built a 5-gene classifier, which predicted outcome with 90% accuracy (89% sensitivity and 91% specificity). Expression of these 5 genes was then measured by qRT-PCR and we derived a 5-gene qRT-PCR risk index. This index predicted outcome with 94% accuracy (93% sensitivity and 95% specificity). We are presently validating this risk index in independent T-ALL patient cohorts.

This work was funded by the National Institutes of Health and the Children's Leukaemia and Cancer Research Foundation.

The relevance of cell lines as a model for drug-resistance in acute lymphoblastic leukaemia

AH Beesley, ML Palmer, J Ford, RE Weller, AJ Cummings, JR Freitas and UR Kees in collaboration with MJ Firth, KU Perera and NH de Klerk, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research.

Cell lines are important models for drug resistance in acute lymphoblastic leukaemia (ALL) but are often criticized as being unrepresentative of primary disease. There are also doubts regarding the authenticity of many lines. We have characterized a panel of ALL cell lines for growth and drug resistance and compared the data to that published for primary patient specimens. In contrast to the convention that cell lines are highly proliferative,

those established in our laboratory grow at rates similar to estimates of leukaemic cells *in vivo* (doubling time 53-442 hours). Authenticity was confirmed by genetic fingerprinting, which also demonstrated the potential stability of long-term cultures. *In vitro* glucocorticoid resistance correlated well with that measured *ex vivo* but all lines were significantly more sensitive to vincristine than primary specimens. Sensitivity to methotrexate was inversely correlated to that of glucocorticoids and L-asparaginase, indicating possible reciprocity in resistance mechanisms. A cell line identified as highly methotrexate resistant (IC50 >8000-fold higher than other lines) was derived from a patient receiving escalating doses of the drug, indicating *in vivo* selection of resistance as a cause of relapse. Many of these lines are suitable as models to study naturally occurring resistance phenotypes in paediatric ALL.

This work was funded by the NHMRC and the Children's Leukaemia and Cancer Research Foundation (CLCRF), Western Australia

Markers of drug-resistance in acute lymphoblastic leukaemia

AH Beesley, ML Palmer, J Ford, RE Weller, JR Freitas, UR Kees in collaboration with MJ Firth, KU Perera and NH de Klerk, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research.

A significant number of patients with acute lymphoblastic leukaemia (ALL) continue to relapse and for these the outlook is dismal due to the development of drug-resistance. 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. Currently, using microarray data generated from our cohort of T-ALL patient specimens, we can predict relapse with >80% accuracy using a 7-drug model derived from our cell line drug-gene profiles. It is anticipated that the genes and pathways identified here will generate novel drug-leads that may contribute to the treatment and prognosis of patients with ALL.

This work was supported by the NHMRC and the Children's Leukaemia and Cancer Research Foundation (CLCRF), Western Australia

[A novel role for the *MLL* gene in steroid resistance in acute lymphoblastic leukaemia](#)

AH Beesley, ML Palmer, J Rampellini and UR Kees, in collaboration with MJ Firth, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research.

Rearrangements of the *MLL* gene, located at chromosome 11q23, are associated with aggressive leukaemias. All children with *MLL*-associated ALL (most of whom are infants) have extremely poor prognosis, although there remains considerable clinical heterogeneity within this cohort. Through its regulation of *HOX* genes, wild-type *MLL* is essential for normal mammalian development and haematopoiesis, yet the locus is highly unstable, with translocations occurring with >30 partner genes on various chromosomes. We have recently studied the resistance of a panel of ALL cell lines to a number of clinically relevant drugs including the steroids dexamethasone and methylprednisolone. Steroids are among the most important classes of drugs used to treat childhood ALL and elevated resistance to them is a feature of relapse. Steroid resistance is also prominent in patients with *MLL* disease. By correlating *in vitro* resistance profiles with gene expression data generated using Affymetrix UI33A microarrays, we have identified a negative correlation between steroid resistance and *MLL* mRNA expression (i.e. high resistance, low *MLL* expression). This was evident in both B- and T-lineage cell lines, but was particularly strong for T-ALL cells ($p < 0.0001$). No karyotypic 11q23 abnormalities were identified in the T-ALL cell lines, consistent with the fact that *MLL* translocations are rare in this lineage. Thus, we hypothesise that steroid resistance is related to reduced expression of the wild-type *MLL* protein. The well-documented steroid resistance observed in patients

with *MLL*-rearrangements may therefore result from a decrease in the expression of wild-type *MLL* following the loss of one allele during translocation. Investigations are underway to more precisely define the *MLL* status of our panel of 22 ALL cell lines, focusing on genetic changes and gene expression. We are altering the expression of the gene in these cells using retrovirally delivered RNAi to monitor the effect on resistance to steroids and other clinically relevant ALL drugs. We are also using a bioinformatics approach to identify genes and pathways that are regulated by *MLL* using our existing microarray data on primary specimens and cell lines. The link between *MLL* expression and steroid resistance is relevant for all patients with ALL, not just those with *MLL* rearrangements, and has important implications for risk stratification and the design of therapeutic protocols.

This work was supported by the Cancer Council of Western Australia, and the Children's Leukaemia and Cancer Research Foundation (CLCRF).

[Glucocorticoid Resistance in T-Lineage Acute Lymphoblastic Leukemia is Associated with a Proliferative Metabolism](#)

AH Beesley, J Ford, RE Weller, JR Freitas, and UR Kees, in collaboration with MJ Firth and KU Perera, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research.

Glucocorticoids (GCs) are one of the most important drug classes for acute lymphoblastic leukemia (ALL), yet despite their clinical importance, the exact mechanisms involved in GC cytotoxicity and the development of resistance remain uncertain. Cell lines represent an important tool to investigate these

mechanisms but many studies rely upon the use of resistant lines developed through extended exposure to high drug concentrations. Such cell lines typically display mutations in the glucocorticoid receptor (GR), something that is rarely found in primary ALL specimens. In view of this it is important to develop *in vitro* models of leukaemia that reflect naturally occurring mechanisms of GC resistance. We have therefore examined the relationship between GR status and GC sensitivity in 15 T-ALL cell lines grown without prior exposure to drugs. In contrast to the contention that that GC resistance *in vitro* almost always arises from mutations in the GR, naturally occurring resistance in our T-ALL panel could not be attributed to mutations in the GR or variations in its level of expression. We conclude that in the absence of selection pressure applied *in vitro*, GR mutation is not a common cause of GC resistance in ALL. Instead, transcriptional profiling indicated GC-resistance in T-ALL is associated with a proliferative phenotype involving up-regulation of glycolysis, oxidative phosphorylation, cholesterol biosynthesis and glutamate metabolism, increased growth rates and activation of PI3K/AKT/mTOR and MYC signaling pathways. Importantly, the presence of these transcriptional signatures in primary ALL specimens significantly predicted patient outcome. We hypothesize that the activation of bioenergetic pathways required for proliferation may suppress apoptotic potential and offset the metabolic crisis initiated in lymphocytes by GC signaling. It is likely that the link between GC resistance and proliferation in T-ALL has not been fully appreciated to date because such effects would be masked in the context of current multi-agent therapies. Our findings warrant the continued development of selective metabolic inhibitors for the treatment of ALL.

This work was supported by the Children's Leukaemia and Cancer Research Foundation (CLCRF), Western Australia

Relapse in children with acute lymphoblastic leukemia involving selection of a preexisting drug-resistant subclone

AH Beesley and UR Kees, in collaboration with S Choi, MJ Henderson, E Kwan, R Sutton, AY Bahar, J Giles, NC Venn, L Dalla Pozza, DL Baker, GM Marshall, M Haber, MD Norris from the Children's Cancer Institute Australia, Sydney

Relapse following remission induction chemotherapy remains a barrier to survival in approximately 20% of children suffering from acute lymphoblastic leukemia (ALL). To investigate the mechanism of relapse, 27 matched diagnosis and relapse ALL samples were analyzed for clonal populations using polymerase chain reaction (PCR)-based detection of multiple antigen receptor gene rearrangements. These clonal markers revealed the emergence of apparently new populations at relapse in 13 patients. More sensitive clone-specific PCR revealed that, in 8 cases, these "relapse clones" were present at diagnosis and a significant relationship existed between presence of the relapse clone at diagnosis and time to first relapse ($P < .007$). Furthermore, in cases where the relapse clone could be quantified, time to first relapse was dependent on the amount of the relapse clone at diagnosis ($r = -0.84$ $P = .018$). This observation, together with demonstrated differential chemosensitivity between subclones at diagnosis, argues against therapy-induced acquired resistance as the mechanism of relapse in the informative patients. Instead these data indicate that relapse in ALL patients may commonly involve selection of a minor intrinsically resistant subclone that is undetectable by routine PCR-based methods. Relapse prediction may

be improved with strategies to detect minor potentially resistant subclones early during treatment, hence allowing intensification of therapy.

This work was supported by the NHMRC, The Cancer Council of New South Wales, The Leukaemia Foundation, the Anthony Rothe Memorial Trust, and The Children's Leukaemia and Cancer Research Foundation, WA.

Xenograft models of infant leukaemia

AH Beesley, DL Baker and UR Kees, in collaboration with MJ Henderson, S Choi, D Wright, RA Papa, A Murch, LJ Campbell, RB Lock, MD Norris, and M Haber from the Children's Cancer Institute Australia, Sydney.

Translocation of the mixed-lineage leukaemia gene (*MLL*) on chromosome 11q23 is associated with 80% of infant acute lymphoblastic leukaemia (ALL) cases. *MLL* rearrangements typically result in the amino-terminal portion of *MLL* being fused to the carboxyl portion of one of more than 50 different partner proteins. Despite intensified treatment, infant ALL patients with *MLL* translocations do extremely poorly, regardless of translocation partner. A better understanding of this particularly aggressive disease is essential for improvements in its treatment and prognosis. Xenografts using cell lines or primary patient material in immunocompromised mice are established as biologically relevant systems to study ALL of infancy and childhood and continuous xenografts in non-obese diabetic severe combine immunodeficient (NOD/SCID) mice promise to be a useful adjunct as they also retain the cytological, immunophenotypic and chemosensitivity profiles of the original patient ALL samples, while providing a renewable source of patient cells. To increase our understanding of *MLL* rearrangements we have been studying the

engraftment of leukaemic cells from an infant ALL patient using the NOD/SCID model. Detailed examination of the cells derived from serial xenograft samples and comparison with patient samples revealed a complex translocation involving *MLL* and loci on chromosomes 2, 13 and 19. This study highlights the merit of utilizing a NOD/SCID xenograft model together with direct examination of patient material to identify novel and complex translocations involving *MLL*. Such complex rearrangements are important to our understanding of infant ALL, yet may be missed in routine clinical investigations.

This work was supported by the NHMRC, The Cancer Council of New South Wales, The Leukaemia Foundation, the Anthony Rothe Memorial Trust, and The Children's Leukaemia and Cancer Research Foundation, WA.

Paediatric brain cancers

The identification of deregulated genes and pathways involved in the pathogenesis of primitive neuroectodermal tumours

PB Dallas, DJ Holthouse, C Bertram, S Egli and UR Kees

Childhood brain tumours are the second most common type of paediatric cancer. Five-year survival rates have remained in the 50-70% range for at least 20 years, and 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 child and family.

The relatively poor outlook for children with brain tumours can be largely explained by the fact that the molecular pathogenesis of primitive neuroectodermal tumours of the central nervous system (CNS-PNETs), the most common type of brain tumour affecting children, is

only partly 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 CNS-PNETs.

CNS-PNETs are thought to arise from the deregulated proliferation of neural stem cells (NSCs) in the developing foetal brain. Hence, the development of CNS-PNETs is likely to be linked to the aberrant activity of signalling pathways that control NSC proliferation and differentiation. As part of our approach to identifying the genes that regulate these signalling pathways, we have analysed chromosomal aberrations in a panel of PNET cell lines using cytogenetic analyses, representational difference analysis (RDA), and microsatellite mapping. This latter work was undertaken in collaboration with the Cancer Genome Project at the Sanger Centre, Cambridge, UK. In addition, in collaboration with Prof. Paul Meltzer from the National Human Genome Institute at the National Institutes of Health in the USA we have assessed our PNET cell lines using array-CGH, a relatively high-resolution cytogenetic analysis technique. 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 five PNET cell lines and a panel of primary CNS-PNET specimens, generated using Affymetrix HG-U133A microarrays. These analyses have led to the identification of several genes of interest that function in the regulation of the cell cycle, embryogenesis, and proliferation. Some of these genes have not previously been linked to CNS-PNET pathogenesis and represent promising new leads for ongoing study.

A neural stem cell for the study of CNS-PNET pathogenesis

C Bertram, S Egli, UR Kees, and PB Dallas

Recent data suggest that many, if not most, cancers arise through the deregulated proliferation of tissue specific stem cells. Some of the strongest evidence supporting this hypothesis has been derived from the study of human brain tumours. Two independent research groups isolated small population of cells from primary CNS-PNETs that had phenotypic and functional similarities to neural stem cells (NSCs). Critically, the capacity to initiate new tumours was restricted to this minority population, indicating that these cells were brain tumour stem cells (BTSCs). In collaboration with Dr Susan Hawes at the Australian Stem Cell Centre at Monash University we are addressing the relationship between NSCs and BTSCs in more detail. As a first step, we are comparing the gene expression profiles of NSCs and CNS-PNETs with the aim of identifying deregulated genes and/or pathways that are linked to CNS-PNET pathogenesis. We have developed an adenovirus-mediated approach for up or down regulating target gene expression in NSCs to study the functional significance of the genes we have identified. This system provides a convenient pipeline for studying the function of any gene or combination of genes linked to CNS-PNET pathogenesis. We anticipate that our NSC model will lead to a clearer understanding of the molecular pathways involved in PNET pathogenesis, and ultimately to the design of new and improved treatment strategies.

The roles of *EZH2* and *FOXO1A* in CNS-PNET pathogenesis

PB Dallas, DJ Holthouse, L Genovesi, S Egli, and UR Kees

A comprehensive molecular analysis of our panel of primary CNS-PNETs and CNS-PNET cell lines identified an oncogene, *EZH2*, and a tumour suppressor gene, *FOXO1A*, which were simultaneously deregulated in the majority of tumour specimens. Importantly, these two genes function in pathways that regulate critical aspects of stem cell growth and differentiation. In collaboration with Dr Susan Hawes at the Australian Stem Cell Centre at Monash University we are assessing the roles of these genes in the regulation of proliferation and differentiation of normal human neural stem cells (NSCs), a cell type from which CNS-PNETs are thought to arise. The manipulation of target gene expression levels in CNS-PNET cell lines and NSCs is being undertaken using adenovirus based over-expression or RNAi knockdown procedures. A detailed understanding of the roles of *EZH2* and *FOXO1A* in CNS-PNET pathogenesis may provide important new clues about molecular approaches to treatment that target biochemical pathways regulated by these two genes.

Staff and Students

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Research Support

Stewart Cattach

Theses passed

Joanne Boag, BSc (Hons), PhD "The molecular characterisation of childhood acute lymphoblastic leukaemia: gene expression profiles to elucidate leukaemogenesis". University of Western Australia.

External Committees

International

Ursula Kees. COG-B946, Children's Oncology Group, USA Chair (2000-)

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

Regional

Ursula Kees. Cancer Council of Western Australia

Invited Presentations

Dr Peter Dallas: Stem cells – what are they and what can they do? Humanist Society Meeting. Perth, February, 2007

Dr Peter Dallas: Childhood Brain Tumours. Telethon Institute for Child Health Research Annual General Meeting, May, 2007.

Dr Alex Beesley: Markers of drug-resistance in acute lymphoblastic leukaemia. Cancer Research Symposium, March 2007.

Dr Ursula Kees: Childhood Cancer. Conference Rotary District 9460, March 2007.

Details of research Funding Awarded in 2007

Research Grant (1 Year), Cancer Council of Western Australia "A Novel Role for the *MLL* Gene in Steroid Resistance in Acute Lymphoblastic Leukaemia".

NHMRC Project Grant 513765 (3 Years) "A Preclinical Model of Relapse in Acute Lymphoblastic Leukaemia".

Division of Clinical Sciences

The Divisional activities centered around three main themes:

1. Asthma

a. Studies on the mechanisms underlying the development of asthma, both in our cohort studies and mechanistic studies in laboratory animals. These studies are largely conducted as part of the Asthma Program grant and NHMRC project grants and involve collaboration between the teams headed by the Program grant PIs: Peter Sly (Clinical Sciences), Pat Holt (Cell Biology); Wayne Thomas (Molecular Biotechnology), Peter Le Souef (UWA School of Paediatrics and Child Health), Steve Stick (Clinical Sciences and PMH Department of Respiratory Medicine), John Upham (Cell Biology) and Phil Stumbles (Cell Biology and Murdoch University). Details of these studies can be found in the sections on Respiratory Physiology and Clinical Asthma Studies.

b. The Global Prevention of Asthma in Children (GPAC) study is funded by the Immune tolerance Network and the National Institute of Allergy and Infectious Diseases, USA and uses oral mucosal immunoprophylaxis (hence forth known as OMIP). This project represents a major collaborative venture between Peter Sly and Pat Holt (Cell Biology). Clinical sites recruiting children are in Perth, Melbourne (Royal Children's Hospital) and New York (Mt. Sinai Hospital). Further details can be obtained from the Division of Cell Biology report.

2. Early Detection of Lung Disease in Cystic Fibrosis

This project, funded largely by the Cystic Fibrosis Foundation Trust, USA, combines the data collected from the Clinically-directed disease surveillance program conducted by the Department of Respiratory Medicine, PHM with the research conducted within Clinical Sciences. The Program is coordinated by Dr. Siobhain Brennan and is run as a collaboration between the Perth Centre (Clinical Sciences and Respiratory Medicine) and the CF clinic at the Royal Children's Hospital Melbourne. This primary aims of this project are to translate research findings into improved clinical care for you children with CF and to determine optimal outcome variables for clinical intervention trials.

3. WHO Collaborating Centre for Research on Children's Environmental Health.

The Division of Clinical Sciences is designated as a WHO Collaborating Centre for Research on Children's Environmental Health in July for an initial period of four years. We are very proud to be one of only two Centres worldwide to include Children's Environmental Health in their designation. The main aims of the Centre are:

- a. To conduct high quality research aimed at understanding the mechanisms underlying the developmental origin of environmental origin in children, with a special emphasis on respiratory diseases.*
- b. To build the research capacity of researchers and health care professionals by providing access to high quality education and training.*
- c. To develop programs and curricula to increase awareness about environmental threats, with special emphasis on respiratory diseases, asthma and allergies in children.*
- d. To develop methods for translating research findings into public policy and intervention strategies.*

The Centre is housed in the Division of Clinical Sciences and affiliated with Curtin University through the Department of Public Health, Division of Health Sciences. The initial Centre staff include: Peter Sly (Director), Felicity Flack (Executive Officer), Merci Kusel (Cohort Studies), Peter Franklin (Environment), Leith Sly (Education and Training), Steve Zubrick (Policy and Planning) and Sue Phillips (Administration). One notable achievement is the development of a Graduate Certificate in Children's Environmental Health, the first such course of its kind anywhere.

Respiratory Physiology

[The influence of VEGF-D on lung growth and development and lung function in health and disease.](#)

Debra Turner, Graeme Zosky, Peter Sly, Teruhiko Sato¹, Marc Achen¹. (¹Ludwig Institute for Cancer Research, Victoria)

The vascular endothelial growth factor (VEGF) family of molecules (VEGF-A, B, C, D, placental growth factor) is important in growth and development of the vascular system (angiogenesis). Research to date has focused heavily on VEGF-A and its role in inflammatory diseases and cancer. New information has revealed that VEGF-D is important in development of the lymphatic system, making it an interesting and important topic of study in the physiology of the respiratory system, where the lymphatic system is an important component of both normal lung homeostasis and in host defense. Lymphatic vessels play an important role in the lung. They are the major vessels responsible for draining fluid from the lungs and are very important in host-defense as inflammatory cells are also cleared from the lungs through them.

The aim of this project is to determine the role of vascular endothelial growth factor D (VEGF-D) in lung function, both in healthy mice and in response to antigen challenge. This research will help us determine what role(s) the lymphatic system plays in respiratory mechanics and specifically examine the role of VEGF-D in maintaining healthy lung function. Mice of different ages will be studied so we can understand the role VEGF-D plays in the developing lung. In 2007 we commenced this project with 21 wild-type controls and 23 VEGF-D knockout mice supplied mice from our collaborators at the Ludwig Institute in Melbourne.

These mice were used for the first phase of the study which involved comparing baseline lung function between VEGF-D knockout mice and wild-type littermate controls. We found no overt differences in lung mechanics, lung volume or the volume dependence of lung mechanics between these groups of mice suggesting that a VEGF-D deficiency does not alter baseline lung function when the lungs are healthy. In 2008 we plan to begin experiments comparing lung responsiveness in these mice using airway disease models.

[Ventilator-associated lung injury in mice: influence of physiological maturity and pre-existing lung injury.](#)

Vincenzo Cannizzaro, Graeme Zosky, Zoltan Hantos, Debra Turner, Peter Sly.

Mechanical ventilation after respiratory failure can be a life-saving intervention. However, mechanical ventilation is known to injure the lungs. In infants and young children, ventilator-associated lung injury (VALI) is a significant problem with long-lasting consequences for the children and their families. VALI is thought to occur as the result of repetitive overstretching and collapsing of the lung, and inflammation. This project was initiated in 2006 with the aim being to develop rodent models of VALI on mice of various ages with and without background lung injuries or complications. We measured lung parameters in 2 week, 4 week and 8 week (adult) old BALB/c mice which were exposed to one of two ventilation protocols (one injurious and one conventional). We found that injurious ventilation caused lung damage in both adult and younger mice (evidence of over distension of the lungs), however conventional ventilation was only damaging to the lungs of adult mice ('stiffening' of the lungs). In 2007 we

found a difference in susceptibility to VALI with younger mice having a much more rapid loss of lung volume on the ventilator than adult mice. We also began measuring I29/Sv mice as part of a study looking at the role of neutrophil enzymes in ventilator induced lung injury which will continue in 2008.

In 2007, we commenced a second limb of this project which was to investigate whether high oxygen concentrations alter respiratory system mechanics and cause lung injury during mechanical ventilation. The project examined whether younger animals (2 week old) are more susceptible to oxygen-induced lung injury when compared with adult (8 week old) animals. Using the low frequency forced oscillation technique no differences were found in airway and lung tissue mechanics between different study groups. The changes of these respiratory mechanical parameters were similar in adult and infant mice. Furthermore, lung and systemic inflammatory response did not differ between treatments in both age groups. Taken together, we found that higher oxygen concentrations did not cause more lung injury when compared to mechanical ventilation with room air. Additionally, infant mice were not more susceptible to oxygen-induced lung injury. Hence, supplemental oxygen can safely be applied during short-term protective mechanical ventilation strategies in infant and adult mice.

Finally, in 2007 a third project was commenced under this area of research aimed at studying effects of different recruitment maneuvers (RM) designed to increase or improve lung volume and lung function, and to better distinguish and understand the mechanisms involved in ventilator induced lung injury (i.e. shear stress, volutrauma, barotrauma, biotrauma, recruitment). We measured lung function in mice using the low frequency forced oscillation technique and we

measured the inflammatory responses to recruitment maneuvers using bronchoalveolar lavage fluid washed from the mouse lungs. We found that "aggressive" and repeated recruitment maneuvers do not cause lung inflammation / injury, but keep the lungs open. In addition, we showed that lung recruitment (opening up of closed or collapsed areas) depends on positive end-expiratory pressure (PEEP) and peak pressure levels. Lastly, the study provides evidence that lung volume standardization at the beginning of an experiment depends on the selected recruitment maneuver and affects respiratory system mechanics. In summary this was a very technical study looking at certain protocol issues that trouble investigations into ventilator induced lung injury. Our results show that RM can be used to help protect against VILI in these short term models, and that standardisation and clear reporting of the protocol is essential to the successful interpretation of these studies.

Allergen-sensitization and environmental exposures in early life interact synergistically to alter lung growth.

Elizabeth Bozanich, Alexander Larcombe, Rosa Gualano¹, Gary Anderson¹, Peter Sly, Debra Turner. (¹University of Melbourne)

Asthma develops as the result of complex interactions between genetic susceptibilities and environmental exposures. Approximately 40% of 6-year-old children in Perth are sensitized to inhaled allergens, however, only half of these have asthma. Allergic sensitization per se is therefore insufficient for the development of persistent asthma. A "second hit", associated with lung inflammation in early life, increases this risk several fold. This "second hit" could come from viral infection or from other inflammatory stimuli such as exposure to cigarette smoke, air pollutants and vehicle exhaust emissions. The timing

of this second hit may well be important, particularly if it is early while the lungs are still growing and developing. Determining the roles viral infection and environmental pollution have early in life may provide us with a strategy for intervention that could prevent life-long changes in respiratory function and airway hyperresponsiveness. The aim of this project is therefore to examine interactions between allergen sensitization and exposure to environmental hazards in early life using a mouse model of allergic inflammation. We will test the hypothesis that the combination of allergic sensitization and *viral infections* in early life alter lung growth, airway function and airway hyperresponsiveness. In contrast, we propose the combination of allergic sensitization and exposure to *non-viral irritants*, such as air pollutants, can not provide the 'second hit' required to induce persistent asthma.

In 2005/2006 we developed a novel model of neonatal allergic sensitization which forms the basis of this project. BALB/c mice are sensitized with ovalbumin (OVA) via the nose on the day of birth and boosted with nasal OVA 4 weeks later. Subsequent exposure to OVA aerosols at 8 weeks of age (ie as an adult) results in heightened airway responsiveness. Recent work has shown that the window of 'opportunity' in terms of successful sensitization is limited to the 48hrs post birth. This preliminary data has formed the basis of a successful three year NHMRC funded project (2007-2009).

In 2007, we confirmed the validity of our neonatal sensitization model with further lung function, assessment of airway hyperresponsiveness (AHR) and inflammation studies. We have also conducted studies in neonatal mice inoculated at 1 week of age with Influenza A, to establish the optimal dose of virus for mild infection in this age group (previously this work had only been done in adults). We have subsequently conducted some preliminary physiology experiments in this age group which are still

be analysed. The next stage of the project will be to bring these two models together and assess the interactions by tracking lung growth and measuring adult AHR. In 2008-2009 we plan to repeat these studies using another respiratory virus, respiratory syncytial virus (RSV), as well as with environmental exposures such as cigarette smoke and diesel exhaust particles.

Mechanisms underlying acute changes in lung function and airway hyperresponsiveness following respiratory viral infections.

Alexander Larcombe, Elizabeth Bozanich, Rosa Gualano¹, Gary Anderson¹, Peter Sly, Debra Turner. (¹University of Melbourne)

This study will investigate the mechanisms responsible for the increased airway responsiveness seen during respiratory viral infections to the common viruses of influenza (flu) and respiratory syncytial virus (RSV). Respiratory viral infections alter lung function and increase airway responsiveness in man. In addition, respiratory viral infections early in life are a risk factor for the subsequent development of asthma. The mechanisms responsible for this are unknown. Both the infecting virus and "host" factors, such as age of infection, gender and genetic predisposition, are likely to be important. These studies will provide a comprehensive assessment of the effects of acute viral respiratory infections on lung function and airway responsiveness using cutting edge techniques developed in our labs. The results will provide new insights into how these infections cause lung disease and may provide clues for new approaches to prevent the adverse effects of these common respiratory viral infections.

We have recently developed mouse models of RSV

and flu. Exposure to both viruses results in AHR to methacholine (MCh), although the pattern of AHR differs depending on the way the MCh is delivered. RSV infected mice show AHR when the MCh is delivered as an aerosol, while infection with flu is associated with AHR to both inhaled and intra venous delivery of MCh. Organ bath studies were able to demonstrate that there was no change to the airway smooth muscle following infection with either virus. Viral titre assays have been able to confirm both excellent levels of infection and clearance in the mice. We have also conducted a number of assays which have given us further insight into the immunology of the model. Data generated from this project formed the basis of a successful three year NHMRC grant (2007-2009).

In 2007, we have measured lung function, responses to methacholine (AHR) and inflammation in adult male and female Balb/c mice infected with influenza when adult, and also in Balb/c mice infected when 7 days old then assessed when adults. In mice infected and tested when adults we found significant inflammation and AHR 4 days after infection which was cleared 21 days after infection. Responses were similar in males and females. In mice inoculated at 1 week of age we conducted preliminary physiology experiments which are still being analysed. In 2008 we plan to test mice infected at 3 weeks of age (post weaning), and to repeat the studies done in 2007 using another respiratory virus, respiratory syncytial virus (RSV). The studies with RSV will allow us to examine the responses of mice to different viruses and hence determine whether AHR is viral-specific.

Murine models of allergic airways inflammation.

Graeme Zosky, Alexander Larcombe, Elizabeth Bozanich, Jennifer Burchell, Debra Turner, Patrick Holt, Deborah Strickland, Matt Wikstrom and Peter Sly.

Murine models have become increasingly popular over recent decades in order to elucidate the pathobiology of asthma. There are a number of variations in the methods for inducing allergic airways sensitisation in mice that involve systemic antigen sensitisation and subsequent antigen challenge of the airways. This work encompasses two main components; the first looking at allergen derived early and late phase responses, and the second to assess subsequent development of airway hyperresponsiveness to inhaled methacholine, in a commonly used mouse and rat model of asthma.

Allergen responses; over the past three years this project has assessed lung mechanics at a number of time points following a single or multiple allergen aerosols. In Balb/c mice, we were able to consistently generate an early phase response (ie bronchoconstriction within 30mins of allergen exposure) following either 1 or 6 ovalbumin (OVA) aerosols, however we were unable to generate consistent late phase responses at 2,4, 6, 8, 12 or 24hrs after allergen exposure. The early phase responses were strain specific in that we could not generate either an early (or a late) phase response in 129/Sv mice nor C57BL/6 mice. Similarly, in rats, we were unable to produce a late phase response after allergen exposure in either PVG/c rats nor BN rats 2, 4 or 6 hours after allergen exposure. Additional experiments also failed to show an early phase response following a single OVA aerosol in BN and PVG/c rats.

Airway hyperresponsiveness; cumulative methacholine challenges were performed on 129/Sv mice and

C57BL/6 mice to characterise lung mechanics and airway hyperresponsiveness. The data from these 2 strains were compared to data generated in 2005 using BALB/c mice. Quite marked strain-related differences were seen in the pattern of physiological, inflammatory and immunological responses. In particular the physiological responses seen in BALB/c mice, but not the other strains, appeared to be linked to activated T cells in the airways. In order to further explore the role of T cells in the development of airway hyperresponsiveness we have developed an adoptive transfer model in collaboration with the Division of Cell Biology whereby T cells from DO11.10 mice which innately recognize OVA were transferred to naïve BALB/c mice. When the recipient BALB/c mice were then challenged with OVA they were found to have airway hyperresponsiveness. Subsequent experiments using antibody transfer suggested that it was activated T cells alone that were driving airway hyperresponsiveness in these models. This work is currently being prepared for publication.

Assessment of respiratory mechanics in rodents.

Graeme Zosky, Alexander Larcombe, Elizabeth Bozanich, Tibor Janosi¹, Debra Turner, Zoltan Hantos, Peter Sly. (¹University of Szeged, Hungary)

This study has been an ongoing collaboration with Prof Zoltan Hantos from the University of Szeged, Hungary, to develop a technique for accurately measuring lung volume in sedated mice and rats using a custom designed whole body plethysmograph. The measurement of lung volume using plethysmography in humans is complex but well established, it was first described by DuBois et al in 1956 (J Clin Invest 1956;35:322-326). Plethysmography involves placing a

person in a chamber and having them take several breaths against a closed shutter using normal breathing. Changes of pressure in the box, brought about by compression and rarefaction of the gas within the chamber during inspiratory efforts, are related to changes in tidal volume. Plethysmography measures the volume of all the gas in the lungs, including any air trapped by closed or narrow airways, thereby providing a valuable method of measuring absolute lung volume and resting end expiratory lung volume, also known as functional residual capacity (FRC). Lung volume has been shown to alter with disease state, airway smooth muscle constriction, anaesthetic level, inflammation and a number of other factors. Assessment of lung volumes using whole body plethysmography in infants has assisted in the study of normal growth and development of pulmonary function and helped the study of therapeutic intervention in various respiratory diseases. Measurements of FRC provide valuable information about alteration of lung function in the disease state. In our laboratory we routinely use rodents to assess the long and short term influences of allergen, virus and bacteria exposure, fibrosis and bronchoconstrictive agents on the lung, but to date we have not been able to measure lung volume in these murine models of airways disease. In 2005 Prof Zoltan Hantos developed a whole body plethysmograph for the mouse and a separate one for the rat. Studies in the mouse proved very successful and we now incorporate the technique into our routine lung function assessment. In 2006 Prof Hantos made modifications to the rat plethysmograph that resulted in successful measurements of lung volume and the subsequent incorporation of lung volume measurements into our routine lung function assessment in the rat. The ability to successfully measure lung volumes in both the mouse and rat provides us with a powerful tool to enhance and improve our standard lung function measurements and provide valuable information on

disease induced lung volume changes in our animal models.

In 2007 we used healthy Balb/c mice for this purpose, although our ultimate intention is to use the technique to assess changes in lung volumes in mouse models of lung disease. Over the past year we used these techniques to investigate whether healthy Balb/c mice possess basal airway smooth muscle tone, akin to humans. The outcome of the study was that both adult male and female Balb/c lack basal airway tone. This has important implications in the use of these mice in studies of chronic obstructive pulmonary disease. Our 2007 findings have been submitted for publication.

[Interface of T regulatory cells, physiology and cytokines in a murine model of asthma.](#)

Jennifer Burchell, Matt Wikstrom¹, Phil Stumbles¹, Debra Turner, Peter Sly (¹Division of Cell Biology, TICHR)

In 2007 Jennifer Burchell completed the experimental side of her PhD work which was aimed at determining the mechanisms involved in allergen-induced suppression of Airway Hyperresponsiveness (AHR), with an emphasis on the role of Dendritic cells (DC) and regulatory T cells (Treg). DC reside in the airways and continuously sample the inhaled air. When they encounter an allergen they capture and internally process it and present small fragments of the allergen to T cells. A subset of these T cells are called regulatory T cells as they have been shown in the literature to suppress allergic or inflammatory responses which ultimately acts to limit the potential damage caused by the immune response. We hypothesized that if we could have a better understanding of the mechanisms of AHR suppression by DC and Treg, this could result in more targeted and therefore improved

therapies for asthmatics.

In 2007 we showed that a single allergen challenge to the airways of sensitised mice results in rapid capture of the antigen in the airways by DC and presentation to T cells, which subsequently divide and release cytokines such as IL-13 and the development of AHR. After repeated (3 week) allergen challenge AHR was suppressed. Interestingly, DC were virtually unable to capture and process allergen in the airways, therefore limiting presentation to T cells and subsequent T cell division and expansion. In addition Treg numbers were significantly elevated, indicating that this T cell subset may be acting to suppress AHR. To further assess the role of Treg in AHR suppression, Treg from 3-week challenged mice (AHR suppressed) were purified and transferred into single-challenged mice (with AHR). Administering Treg to mice with established allergic airway disease completely suppressed AHR. Furthermore depletion of Treg in 3-week challenged mice (AHR suppressed) restored AHR. From this we conclude that Treg are necessary in allergen-induced suppression of AHR and that Treg can mediate the suppression of AHR via modulation of antigen-handling by airway DC.

Internal collaborations

Throughout 2007 we have been involved in several ongoing collaborative research projects within the Telethon ICHR. These projects are written up in greater detail elsewhere within this annual report by our collaborators, noted in parenthesis below. In brief we have assessed airway and tissue mechanics in the following collaborative studies;

- Immunomodulatory effects of ultraviolet B (UVB) radiation in mice (with Dr Prue Hart, Division of Molecular Biotechnology)

- Airway mucosal DC maturation is controlled by local T cell interactions following repeated antigen challenge (with Deborah Strickland and Patrick Holt, Division of Cell Biology)
- Characterisation of mouse respiratory tract antigen presenting cell (RT-APC) populations and their response during allergic airway inflammation (Matt Wikstrom and Phil Stumbles, Division of Cell Biology)
- Interface of T regulatory cells, physiology and cytokines in a murine model of asthma (PhD work of Jennifer Burchell in collaboration with Matt Wikstrom and Phil Stumbles, Division of Cell Biology)
- Potential to boost airway mucosal T regulatory cell number and function, in a rat model of OVA induced experimental allergic airways inflammation, by oral administration of OM Pharma-85 (with Deborah Strickland and Patrick Holt, Division of Cell Biology)

Clinical Asthma Studies

Role of early, repeated viral respiratory infections and the development of atopy in childhood (The Childhood Asthma Study).

Merci MH Kusel, Peter D Sly, Patrick G Holt & Richard Loh

263 children at high genetic risk of atopy were recruited between 1996-98 and closely followed till they reached 5 years of age. Extensive data on early respiratory infections, wheezing and development of atopic diseases such as eczema and asthma was collected during the first phase of the study which was

completed in 2003. The 10-year old follow-up visit commenced in July 2006 and will be completed by August 2008. At this visit, children undergo extensive lung function testing as well as blood and skin prick tests to determine their atopic status. Data on exposure to environmental pollutants such as pesticides, as well as dietary information has also been collected by face to face interviews. Our understanding of the development of innate and adaptive immune processes as well as factors determining the development and maturation of the immune system will be further enhanced by data collected during this visit.

The ongoing contribution and support by the study children and their families is acknowledged.

Clinical Respiratory Physiology

Group Leader: A/Prof Graham Hall (Senior Respiratory Scientist, PMH and Honorary Research Fellow, ICHR)

Clinical Sciences has an active collaboration with the Department of Respiratory Medicine at Princess Margaret Hospital (PMH) and the School of Paediatrics and Child Health (SPACH), UWA in a number of studies in which respiratory physiology is a major study outcome. These are summarised below.

Lung function outcomes in infants and preschool diagnosed with Cystic Fibrosis

Graham Hall, Gary Nolan, Catherine Gangell, Siobhain Brennan, Stephen M Stick and Peter D. Sly for the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF)

This area of research aims to characterise the onset of early lung disease in infants and young children

with cystic fibrosis. We are monitoring lung function in all infants diagnosed with cystic fibrosis at birth in conjunction with the Royal Children's Hospital Melbourne. A uniform and standardised protocol for both infant and pre-school lung function testing is now well-established. In infants lung function testing involves the multiple breath washout test (MBW), and the low frequency forced-oscillation technique (LFOT). From these two tests, information regarding lung volume, ventilation inhomogeneity, airway resistance and tissue mechanics have been deduced. In pre-school children lung function is measured using the Forced oscillation technique. The forced oscillation technique (FOT) requires minimal co-operation from young children and can be routinely used in a clinical setting. Both cross-sectional and longitudinal data have been obtained. Data are being compared to bronchoscopies, bronchial alveolar lavage and computed tomography scans as well as blood, genetics and urine sampling.

Antecedents of childhood asthma: Do measurements of infant lung function and airway inflammation help predict childhood asthma?

Peter Franklin (SPACH), Vaska Stavreska, Graham L. Hall, Stephen M. Stick

Exhaled nitric oxide may reflect airway inflammation in asthma. We have developed a technique for measuring exhaled nitric oxide in infants as it is possible that this may be a useful test for asthmatic wheeze in this age group. We measured FENO and lung function in approximately 140 wheezy and non-wheezy infants. These children are being re-assessed at age 7. The aim of the study is to investigate if measurements of lung function and airway inflammation in infancy are predictive of the development of childhood asthma at

seven years of age. To date approximately 110 children have returned for lung function, nitric oxide and allergy tests.

Investigation of exhaled temperature as a non-invasive marker of airway inflammation in children

Graham Hall, Karla Logie, Smilja Dragovic, Merci Kusel, Peter Sly

This study aims to further investigate the use of exhaled breath temperature as a potential indicator of airway inflammation in children. The study's primary focus is to investigate the potential influences of the underlying lung physiology (lung volumes and disease history) and ambient conditions on exhaled breath temperature.

To date, children involved in the Childhood Asthma Study (CAS) have been studied. Of the children involved in the study thus far, acceptable and reproducible data has been obtained in 86% of children. We have found that:

- Room temperature significantly influences all aspects of the exhaled breath temperature profile
- Vital capacity strongly influences exhaled breath temperature in healthy children
- After accounting for room temperature and lung volume, atopy, hayfever and airway hyper-responsiveness had no statistically significant influence on exhaled breath temperature.

The application and feasibility of flow independent FENO models in children.

Graham Hall, Claire Shackleton, Smilja Dragovic, Merci Kusel, Peter Sly

Measurements of exhaled Nitric Oxide (FENO) have been proposed for the non-invasive measurement of airway inflammation. FENO measurements using multiple exhalation flows allow measurements of both airway and alveolar compartments through the application of NO exchange models. This study aimed to investigate the feasibility and application of NO exchange models and the influence of pathophysiological factors on measurements of FENO and NO model variables. 76 children involved in the Childhood Asthma Study (CAS) have been studied at four exhalation flows, skin prick tests, spirometry and methacholine challenge testing. NO model variables were assessed through application of the Tsoukias and Silkoff NO exchange models. The Tsoukias model was valid in only four children, while the Silkoff model was valid in 38 children and in multiple linear regression analysis variables were significantly influenced by atopy ($p < 0.001$) alone. Measurements of FENO at 10 and 50ml/s showed a strong correlation with Silkoff model variables. FENO measurements at high exhalation flows were not feasible in this study population, questioning suitability of models requiring high flows. Strong correlations between exhalation flow and Silkoff airway model variables suggest no advantage to multiple exhalation measurements in young children to measure airway NO variables.

Cystic Fibrosis

Early detection of inflammation in cystic fibrosis.

S Brennan, PD Sly, SM Stick, GL Hall, S. Ranganathan, P. Robinson, C. Robertson, C. Murray

In 2007 this research group continued investigations in the area of early development of inflammation and infection in cystic fibrosis. This project has now been extended to include a site at the Royal Children's Hospital in Melbourne and continued to receive funding from the US. Cystic Fibrosis Foundation. This project aims to investigate the following:

1. To characterise the inflammatory response in the lungs of infants and young children with CF and to correlate this with bacteriology, clinical status and lung function.
2. To determine whether the inflammatory markers assessed are predictive of long term outcome in these children.
3. To investigate the nature of the relationship between markers of lung disease and the breakdown products of lung tissue excreted by the kidneys.

Our findings to date are outlined below:

- Over Four hundred broncho-alveolar lavage fluid samples have been collected from over 100 children with CF. Inflammation is evident in virtually all of the lavage fluids collected, even in the very young infants (from four weeks of age) with no apparent clinical symptoms or infection.
- It appears that once acquired, inflammation consistently tracks with infection.
- The level of acquisition of *Staphylococcus* and

Haemophilus is lower in this cohort than compared with other national CF centres for the same age group. This may be a consequence of the prophylactic antibiotic policy in the WA paediatric clinic.

- Whilst there appears to be no difference in the age of acquisition in *Pseudomonas* in our clinic compared with the other national CF centers, the lavage program has demonstrated some success at eradicating *Pseudomonas aeruginosa* in young children with CF with successful eradication being achieved in over 88% of children treated.
- We have incorporated results from a high resolution computer tomography (HRCT) measure in our database and have found that structural lung disease (bronchiectasis) can be identified in children with CF as young as 3 months of age and is not uncommon (approximately 30%) in children three years and over. This data is currently being used to support an international collaboration for therapeutic interventions to occur in pre-school children. This is a paradigm shift for clinicians and research in CF research as most clinical trials are designed for children over six years of age.

We have an extensive working database for the analysis of this data, and have begun to analyse and publish longitudinal trends of disease progression in these children identifying the factors that most significantly contribute to disease outcomes.

Numerous collaborations (national and international) have resulted from this ongoing study.

Inflammation in cystic fibrosis: Friend or Foe?

PD Sly, S Brennan, K. Winfield

In cystic fibrosis, inflammation and infection occur concurrently, the role of inflammation is to attack invading pathogens and to effectively remove them from the host. In CF, for various reasons, inflammation overwhelms the lungs and the abundant neutrophils release excessive levels of enzymes (such as elastase) that can also attack lung tissue proteins elastin and collagen. It is this collateral damage from inflammation and infection that initiates fibrotic lesions, leading to long term irreversible lung damage and pulmonary function decline. In 2001, we initiated a new study that we believe may provide important information to the CF community about when inflammation begins to attack lung tissue. This study may provide a solid rationale for the use of anti-inflammatory therapy in CF and may also provide a non-invasive method that could be used to determine the point in disease when that anti-inflammatory therapy is warranted.

The study involves the recruitment of children with CF and children with no history of lung disease for our control population. We have recruited children for this study from both the Perth clinics and schools, as well as other national CF centres. We have investigated the breakdown products of elastin and collagen fibres found in urine and measured by high performance liquid chromatography (HPLC) to see if they correlate with the inflammation measured from sputum or bronchoalveolar lavage in patients at times of stable clinical health and at times of exacerbation of disease. We are also investigating whether current iv. treatments, or anti-inflammatory therapies currently being trailed in the CF community locally and nationally, will influence these levels.

This study received funding from the National Cystic Fibrosis Association for 2002 and the first journal article outlining the validation of the technique and describing the effect of age in a non-CF pediatric population has been written by Ms Kaye Winfield and accepted for publication in the Annals of Clinical Biochemistry.

A second article was prepared from this work that showed that urinary desmosines are increased in children with CF who have a current exacerbation of their lung disease, indicating that at this time, tissue degradation is occurring. Desmosines were effectively reduced with in-patient treatment. This work is currently under review by a Thoracic Journal.

Collaborations that have resulted from this work include:

- (1) Investigation of correlation of biochemical markers of oxidative stress in patients with CF. Working with Dr. Tony Kettle of Christchurch New Zealand, we have established a collaboration to concurrently assess markers of tissue damage alongside established markers of oxidative stress (tyrosine residues). This will provide us with further information about the process of early inflammatory-led damage in children with CF.
- (2) Collaboration with Dr. Yvonne Belis, Westmead children's hospital investigating the effect of reflux on markers of lung inflammation.

Ms. Winfield submitted her masters thesis in this area which was passed in 2007.

Immune Surveillance in cystic fibrosis- the role of macrophages and dendritic cells.

S. Brennan, J. Upham, M. Wikstrom, , PD Sly

In collaboration with Dr. John Upham, of the Cell Biology Division, we have investigated the role of antigen presenting cells in the early stages of cystic fibrosis lung development. This study involves assessment of blood dendritic cells and monocytes, as well as macrophages found in the bronchoalveolar lavage fluid of children with CF. Children with CF have recurrent infections, which are often difficult to clear and we hypothesise that one reason for this is that there is a dysregulation of the "surveillance" system, which involves the antigen presenting cells in the airways- the dendritic cells and macrophages. With the assistance of the respiratory fellows in respiratory Medicine (Dr. Tonia Douglas, Andres Shultz and Paul McNemara) we use cells from BAL and collect blood from children with CF undergoing BAL, and will also be collecting blood from non-CF children undergoing surgery for non-respiratory related reasons. This study investigated the presence, of macrophages in the lungs and the presence of dendritic cells and monocytes in the blood using flow cytometry and in-vitro culture techniques. We also investigated the presence of chemokines (proteins responsible for recruiting macrophages and dendritic cells to the lungs) and found these highly elevated in young uninfected children with CF. In addition we have investigated the expression and activity of TLR2 and TLR4 receptors on monocytes in the blood and on macrophages in the lung.

This study began in late 2003, and received funding from the Australian cystic Fibrosis Research Trust for 2004. The findings of this study are being prepared as two publications.

The findings from this study were that although there

were no apparent differences in dendritic cell subtypes in CF and non-CF subjects, there were significantly more macrophages in lungs of young children with CF, and that these were related to the high levels of CC chemokines (attractant proteins), present in CF lungs. These findings are currently under consideration for publication.

The value of serum antibodies to *Pseudomonas Aeruginosa* Exotoxin A as markers of early *Pseudomonas* infection in young children with cystic fibrosis

T. Douglas, S. Brennan, PD Sly

This pilot study aimed to investigate the value of *Pseudomonas aeruginosa* antibody levels as markers of early respiratory infection with *Pseudomonas aeruginosa* and response to treatment in young children with cystic fibrosis (CF). *Pseudomonas aeruginosa* (*Ps a*) is a primary CF pathogen that accelerates lung disease and increases mortality. Initial "intermittent" infection with *pseudomonas* is potentially treatable if detected before chronic infection is established. Currently detecting early respiratory infection reliably in young children with CF requires bronchoscopy under general anaesthesia. Less invasive methods of sampling respiratory secretions in children such as oro-pharyngeal swabs are insensitive and do not reflect lower respiratory bacteria accurately. Infection with *Ps a* stimulates the production of antibodies to *Ps a* proteins and toxins that are detectable in the serum. Levels of these antibodies in children were found to be sensitive markers of early *Pseudomonas* infection in the lungs, and response to anti-*pseudomonas* treatment, they may be useful in management of lung disease and may reduce the need for more invasive surveillance. However, studies investigating the potential of these markers in young children are scarce. The Respiratory Department at PMH has an established bronchoscopy program for all

children in WA with CF and offers each child an annual bronchoscopy and bronchial lavage (washings) until around the age of 6 years. This unique program permits the study and treatment of respiratory infection and inflammation in children too young to expectorate or cooperate with conventional methods of lung surveillance. The potential of antibodies to *Pseudomonas* as markers of respiratory infection can therefore be assessed and, in this study, compared with the "gold standard" of bronchial lavage throughout early childhood. Data from this study will determine whether a larger prospective study is warranted and the sample size required.

This pilot study was funded by the Princess Margaret Hospital seeding grants scheme, and formed the basis of a successful postgraduate diploma project which was conducted in 2006 by Mr Charles Goh, through the Department of Pathology, UWA.

This pilot study was used to form the basis of a national CF research trust grant, submitted in June 2006, which was successfully funded for 2007. The grant was extended to include analysis of all Perth samples and to analyse samples collected from a national CF BAL program for antibody titres to *Pseudomonas aeruginosa*.

The results of this study were that while serum antibodies to *Pseudomonas aeruginosa* were reliably measured in CF serum in both a discovery and a test cohort, the presence and levels of the serum antibodies did not accurately identify whether a child had a *pseudomonas aeruginosa* infection in the lung. However, the absence of serum antibodies to *Pseudomonas aeruginosa* may provide some clinical usefulness at ruling out a chest infection.

This study was extended to investigate whether salivary antibodies (a less invasive method) would be more sensitive at detection of *Pseudomonas aeruginosa*. This study has received funding from The Princess Margaret

Hospital Foundation and is spearheaded by Dr. Tonia Douglas. This study will involve the collection of saliva from children with CF and from age matched healthy controls. This project will continue through 2008.

Investigating markers of oxidative stress in young children with cystic fibrosis: a driving mechanism of pulmonary inflammation?

Brennan, S, Kettle, Sly, PD, Cooke, M, and Grigg, J

Previous preliminary data collected in association with Prof Kettle (NZ) on the presence of oxidative stress in young children with CF was used in a recent grant submission to the Australian Respiratory Council. The success of this grant application for 2007 will allow us to further investigate the role of oxidative stress in driving pulmonary disease by measuring biomarkers of reactive oxygen species and antioxidants in the lungs of young children with cystic fibrosis (CF) and relating these to pulmonary inflammation, infection and clinical outcome. Based on our preliminary data we believe that oxidative stress is initiated very early in CF and that it contributes significantly to the high inflammatory burden so common in lungs of children with CF. Recent pilot studies also report that inhalations of the anti-oxidant glutathione (GSH) are associated with improved lung function in older children and young adults with CF. The usefulness of such a therapy would be optimal if implemented at the time of when oxidative stress begins. Therefore a full understanding of the functional maturation of antioxidant defences and of the development of oxidative stress in these preschool children from birth is essential.

The results of this study have shown that oxidative stress is present in children with CF and is related

to both the level of inflammation in the lungs and to the structural damage (bronchiectasis) that we are able to now see on HRCT. This study has been is to be presented as an oral presentation at the Thoracic Society for Australia and New Zealand in March 2008.

This study has been extended to investigate the presence of markers of oxidative stress in urine in young children with CF and to investigate how this relates to clinical outcomes. This study is conducted in collaboration with Dr. Marcus Cooke and Dr. Jonathon Grigg in the UK and Assoc. Prof Tony Kettle in New Zealand and has received funding from the Australian Cystic Fibrosis Research Trust and UWA small research grants scheme for both the clinical and the research components.

Other Research

Promoting Assent: Involving Children in the Decision-Making Process in therapeutic Clinical Trials.

Angela Allesandri, Linda Kristiansen¹, Peter D Sly.
¹Curtin University of Technology.

Dr. Angela Allesandri, a clinical oncologist at PMH, is undertaking studies towards a PhD in the important area of children's assent to participate in therapeutic clinical trials. While this is a new area of research for the Division, it builds on the interests and involvement of Peter Sly in the human ethics committee at PMH.

Staff and Students

Head of Division

Peter D Sly MD MBBS DSc FRACP

Professor, School of Paediatrics & Child Health, University of Western Australia

Respiratory Physician, Princess Margaret Hospital for Children

Director, WHO Collaborating Centre for Research on Children's Environmental Health.

Adjunct Professor, School of Public Health, Curtin University of Technology.

Research Staff

Vincenzo Cannizzaro MD

K.E (Bill) Finucane (Emeritus Professor)

Zoltan Hantos PhD (Perpetual Visiting Professor, Adjunct Professor UWA)

Alex Larcombe (PhD)

Debra J Turner PhD (Program Coordinator of Respiratory Physiology Research, Adjunct Senior Lecturer UWA)

Graeme Zosky (PhD)

Siobhain Brennan PhD

Claudia Calogero MD

Tonia Douglas MBChB MRCPCH

Carlie Dunford BSc

Felicity S Flack PhD

Catherine Gangell

Luke Garratt

Merci Kusel MBBS PhD

Britta von Ungern Sternberg

Kaye Winfield BSc

Postgraduate Students

Angela Alessandri MBBS FRACP (Paeds), MBioeth PhD Candidate

Tonia Douglas MBChB (Hons), MRCPCH (UK) PhD Candidate

Lisha van Reyk BSc(Hons) PhD Candidate

Elizabeth Bozanich BSc (Hons)

Jennifer Burchell BSc(Hons) PhD Candidate

Research Support

Luke Berry

Cameron Brooke

Smilja Drogovich BPsych

Samantha Gard Dip Tech (Applied Science)

Jessica Lynch BSc

Susan Phillips BA

Theses passed

Jackie M Cesareo BA (Hons) PhD Candidate (in conjunction with UWA Psychology) "Psychosocial stress and health-related outcomes in chronic childhood asthma : using a biopsychosocial approach to understand transactional relationships across childhood and adolescence".

Marie Deverell BSc (Hons) PhD Candidate "Risk factors

for persistent asthma in adolescents : a community based longitudinal birth cohort".

Kaye Winfield BSc. Masters Candidate "Extraction of desmosines from urine: an indicator for inflammatory lung damage".

Angela Chan Ph) Functional assays for genes involved in thymocyte development and haemopoiesis.

Awards

Alexander Larcombe, TSANZ travel award 2007

Alexander Larcombe, APSR travel award 2007

Graeme Zosky, APSR travel award 2007

Graeme Zosky, Pfizer Biostatistics Collaborations of Australia Award for Excellence

Jennifer Burchell, TSANZ travel award 2007

Jennifer Burchell, TSANZ best oral award in Cell Biology and Immunology SIG 2007

Jennifer Burchell, ASI travel award 2007

Jennifer Burchell, AFWA travel award to attend the International Congress of Immunology in Rio de Janeiro, Brazil (partial funding)

Jennifer Burchell, Friends of TICHR travel award to attend the International Congress of Immunology in Rio de Janeiro, Brazil (partial funding)

Jennifer Burchell, Young Investigator Award for best oral presentation at the TSANZ (WA) scientific meeting 2007.

Elizabeth Bozanich, Asthma Foundation of WA PhD Scholarship

Elizabeth Bozanich, TSANZ travel award 2007

External Committees

International

Peter Sly Pacific Basin Consortium on Environment and Health.

Peter Sly World Health Organization, National Institute of Environmental Health Sciences Collaborative Agreement Scientific Advisory Committee

Peter Sly World Health Organization Long-term Children's Study Advisory Group

Peter Sly Canadian Healthy Infant Longitudinal Development (CHILD) Study

Peter Sly Pediatric Organization for Worldwide Respiratory Research

Peter Sly National Institute of Environmental Health and Sciences

Peter Sly Program Committees for International Scientific Meetings:

- International Society of Environmental Epidemiology, Mexico City 2007
- Pacific Basin consortium for Environment and Health, Beijing 2007
- Asian Pacific Society of Respirology, Gold Coast QLD, 2007

National

Peter Sly Asthma Australian Medical and Scientific Advisory Committee

Regional

Peter Sly Intellectual Property Management Group, Department of Health WA

Peter Sly Telethon Institute for Child Health Research Executive Committee

Peter Sly Human Ethics Committee, Princess Margaret Hospital for Children

Peter Sly Chairman Scientific Advisory Subcommittee, Human Ethics Committee, Princess Margaret Hospital for Children.

Peter Sly Chairman Scientific Advisory Committee, Animal Experimentation Committee, Telethon Institute for Child Health Research

Peter Sly Asthma Foundation of Western Australia Medical Advisory Committee

Peter Sly Research Leaders Forum, University of WA
Debra Turner Board of Directors, Scitech, Western Australia

Debra Turner Executive Committee of Thoracic Society of Australia and New Zealand (WA branch)

Merci Kusel Board Member, Starlight Children's Foundation (National and WA Boards)

Elizabeth Bozanich Associates Committee of Thoracic Society of Australia and New Zealand (WA branch)

Jennifer Burchell Associates Committee of Thoracic Society of Australia and New Zealand (WA branch)

Invited Presentations

Debra Turner Lung Institute of Western Australia Lung Symposium, November 5th 2007, Perth. "Animal models and bronchial reactivity".

Peter Sly To Wheeze or Not To Wheeze: What Are the Mechanisms? Ann Woolcock Memorial Lecture, Asian

Pacific Society of Respiriology 2007 Congress, Gold Coast, Australia.

Peter Sly Environmental Impact on Pediatric Lung Health. American Thoracic Society International Conference. San Francisco, May 2007

Peter Sly Oscillation Mechanics of the Respiratory System: Basic Research and Clinical Applications. American Thoracic Society International Conference. San Francisco, May 2007

Peter Sly Early life events: development of the immune system, allergen exposure. World Asthma Meeting, Istanbul June 2007

Peter Sly What medications are useful in the treatment of preschool wheeze? World Asthma Meeting, Istanbul June 2007

Peter Sly New biomarkers of environmentally-related respiratory effects in children. ISEE Mexico City Sept 2007

Peter Sly Lung Development and window of susceptibility. ISEE Mexico City Sept 2007

Peter Sly Science to Action – Future Immunotherapy. Asian Pacific Society of Respiriology 2007 Congress, Gold Coast, Australia.

Peter Sly Vulnerability of Children to Exposure to Air Pollution. Asian Pacific Society of Respiriology 2007 Congress, Gold Coast, Australia.

Peter Sly Inflammation, infection and early lung damage. ERS Research Seminar, Leuven, Belgium, Feb 2007

Peter Sly Development-stage susceptibility of the respiratory and immune system. ISEE Mexico City, Sept 2007

Peter Sly Measuring health consequences of exposure to air toxicants. ISEE Mexico City, Sept 2007

Peter Sly An Immunoepidemiological approach to asthma. Korean Academy of Pediatric Allergy and Respiratory Disease (KAPARD) Seoul, April 2007

Peter Sly Predicting which children will develop asthma. Asthma and Allergy Birth Cohort Symposium. Seoul April 2007

Peter Sly Susceptibility of Children to Environmental Pollutants. Australian Institute of Environmental Health (WA/NT Branch), Perth May 2007

Peter Sly Susceptibility of Children to Environmental Pollutants. Symposium "The Environment And It's Impact On Our Children's Health", Telethon Institute for Child Health Research, Perth, March 2007

Leith Sly Education in Children's Environmental Health. Asian Pacific Society of Respiriology 2007 Congress, Gold Coast, Australia.

Merci Kusel Antibiotic use in the 1st year of life and risk of atopic disease in early childhood. Asian Pacific Society of Respiriology 2007 Congress, Gold Coast, Australia

Merci Kusel Early respiratory viral infections, atopic sensitisation and risk of subsequent development of persistent asthma. Asian Pacific Society of Respiriology 2007 Congress, Gold Coast, Australia. This presentation won the Best Presentation in the Environmental and Occupational Health & Epidemiology Assembly of the APSR Conference

Division of Molecular Biotechnology

Research in the Division of Molecular Biotechnology encompasses studies on the mechanisms of inflammation and allergy and the development of methods to treat or prevent diseases resulting from these processes.

Allergen Group: The allergy research in Molecular Biotechnology investigates 1) the development of improved immunotherapy with molecularly defined allergens and molecularly engineered derivatives of allergens, 2) comparisons of immune responses to defined allergens to elucidate the differences between responses that lead to allergy and responses that do not, and 3) since many people with severe allergy do not develop disease, the study of other mucosal immune responses that could influence the pathogenesis.

*The studies have focussed on house dust mite allergy, which is the most important source of allergy worldwide and in Australia, and for comparison allergy to cats, which shows several differences in the sensitisation process. The characterisation of cat allergens and the responses that they induce is also a neglected area of investigation such that the current clinical assessment of the severity of the allergy may be compromised by the use of extracts that do not contain effective amounts of all of the important allergens. The study of responses to other mucosal antigens has examined responses to common mucosal colonising bacteria *Haemophilus influenzae* and is now being extended to *Streptococcus pneumoniae*. In order to investigate questions that cannot be examined in humans murine models of inhalation allergy to house dust mite allergen homologue papain and mucosal infection with *Pasteurella pneumotropica* have been developed*

Inflammation Group: Members of the Inflammation Research Group are elucidating the mechanisms by which the UVB wavelengths in sunlight can modulate immune responses. UV exposure is one of the most important environmental factors affecting man. We know that UV exposure can initiate skin cancers but it is because of a suppressed immune system that these cancers develop and grow and are not immunologically rejected. The UV-induced suppression of the immune system is systemic and causes reduced responses to allergens delivered to the airways. The results have been consistent in two models of respiratory airways disease in mice in which UV irradiation of skin reduces some of the hallmark symptoms of asthma. We have shown that UV-irradiation of skin causes the induction of regulatory cells which when transferred into new mice can modulate immune responses to respiratory allergens. Extensive studies are ongoing in an attempt to identify and characterise these cells and their mode of action. Studies are also focussing on the immunological potency of vitamin D that is formed in UV-irradiated skin. As a model we paint the active vitamin D on skin and investigate the immunological consequences. In other studies we are investigating the effect of UV irradiation of skin on cells in the bone marrow. Our studies suggest

that if we deliver sufficient UV rays to the shaved skin of mice to cause some inflammation (similar to a sunburn), the bone marrow is stimulated to produce greater numbers of cells which in turn would be attracted back to the inflamed skin site. However, as a homeostatic or compensatory response, these cells may not have reduced immune potential.

In a second stream of research, Members of the Inflammation Research Group are studying the mechanisms by which anti-inflammatory cytokines can regulate the production of inflammatory mediators by human macrophages and other cells of the monocyte lineage. We have previously identified new molecules rapidly produced in human monocytes exposed to the anti-inflammatory cytokine, interleukin-4. In 2007, our studies concentrated on examining the regulatory function of suppressor of cytokine signalling-1 (SOCS-1) as a molecule rapidly induced by interleukin-4 and perhaps representing an important mechanism of control by interleukin-4. It has been necessary to infect monocytes and macrophages with a SOCS-1-encoding virus and then to examine inflammatory mediator production by these infected cells. Studies to examine the anti-inflammatory properties of SOCS-1 and other similar proteins are continuing in human blood monocytes, and inflammatory cells isolated from the fluid drained from swollen knees of patients with inflammatory arthritis. These cells are important as it is these inflammatory cells that must be regulated during inflammation.

Allergy

Antibody responses to allergens and bacterial antigens in children during asthma exacerbations and recovery. [_____](#)

BJ Hales, L. Pearce, L A Hazell, W Smith, W. R. Thomas with Dr A. Martin Princess Margaret Hospital and Professor P. N. LeSouef, Dr I. A. Liang and Dr C. M. Hayden UWA School of Paediatrics and Child Health.

The IgE anti house dust mite antibody responses of children attending an emergency department for the treatment of asthma attacks were indistinguishable from the responses of children recruited from a community cohort by the presence of skin test reactivity. They had the same titres and predominance of responses to the major Der p 1 and 2 allergens, and from a study of panel of 9 allergens showed no increase in the response to other allergens. Children recruited with exacerbation however had almost a complete absence of IgG1 and IgG4 antibody normally associated with allergy. Follow up measurements after recovery showed lower but still high IgE anti-allergen titres and no restoration of IgG antibody. About half of the exacerbations were associated with a rhinovirus infection but there was no difference in the IgE responses with and without infection. The most consistent change in recovery was an increase in the IgE antibody titre to the P6 antigen of *Haemophilus influenzae* possibly induced by a recrudescence of a low level infection. The measurement of the antibacterial titres also revealed that children with exacerbation had lower IgG1 antibody titres to the P6 antigen and that 25% had undetectable levels of a response readily found in all healthy children. The results show susceptibility of allergic children to asthma exacerbation is associated with defects in anti-microbial and not anti-allergen responses although the influence of the allergy on anti-microbial immunity is unknown.

Defective anti-bacterial responses of asthmatic children in infancy

B. J. Hales, L. J. Pearce, L. A. Hazell, W. R. Thomas with M.M.H. Kusel, P. D. Sly and P. G. Holt from Cell Biology and Clinical Sciences

Quantitative antibody microtitre assays with the protective P6 antigen of *Haemophilus influenzae* have been developed so that accurate measurements can be made of anti microbial immunity at the respiratory mucosa. The responses to this antigen are typically induced by non-clinical colonising infection and are important to protect from pathogenic effects of repeated infection with the ubiquitous non-typeable isolates. The possibility that important differences would be detected in atopic and non-atopic people was first shown by the finding that anti-P6 antibodies of the strictly Th2-dependent IgG4 isotype were found in atopic but not atopic children and adults. Further analysis has shown that although this was significant for both males and females that there was a strong bias to males, a finding of interest given the male bias to asthma in infancy. It is now shown with both a pilot and a comprehensive study of a childhood asthma cohort that 2 year-old infants that develop allergy have markedly low IgG1 antibody titres to P6. Since allergy to inhalant allergens has not been developed at 2 years of age the decreased response is not due to the allergy but could be due to the antecedents of the allergy, have a causal effect on allergy or be a measure of generally altered immune responses of children at risk of developing allergy. The revelation of low immune responses to a conserved antigen of a ubiquitously colonising organism provides a highly accessible window that can be used to study differences in the adaptive immune responses of children that develop allergy.

Interaction of allergic sensitisation and *Pasteurella pneumotropica* infection in mice.

S. B. See and W. R. Thomas

Pasteurella pneumotropica naturally infects the mucosa of mice in a similar fashion to the infection of humans with *Haemophilus influenzae*. The characterisation of its outer membrane protein antigens P4, P6, P26 and D15 has previously been reported as well as immune responses to these proteins and the vaccine potential of the P4 and P6 antigens. Allergic responses induced in mice sensitised by the inhalation of the papain allergen have now been shown to have at least two different effects on this infection. Firstly allergic reactions in mice that had recovered from infection induced a transient recurrence of the infection in the lungs an event consistent with notion that allergy may increase susceptibility to infection. In contrast, sensitised mice infected with *P. pneumotropica* shortly after recovering from an allergic reaction had increased resistance to the infection and made higher IgG antibody responses including the Th1 dependent subclass. The pre-existence of a Th2 response to an allergen therefore does not lead to decreased antibacterial immunity.

Species specificity of anti-house dust mite antibodies to important allergens.

B. J. Hales, L. J. Pearce, L. A. Hazell, W. R. Thomas, T. K. Heinrich and W. Smith with N. Malainual and P. Vichyanond, Mahidol University, Bangkok

The 2 most important species of pyroglyphid house dust mites are *Dermatophagoides pteronyssinus* and *D. farinae*. While it is known that IgE antibody to allergens of both species cross-reacts the degree to

which occurs is not known. Other studies have either not used quantitative techniques or have used sera from people living in geographical regions with both of the species. Here natural group 1 and 2 allergens and recombinant group 5 and 7 allergens have been used to measure IgE titres with sera from people in Perth who are only exposed to *D. pteronyssinus*. On average titres of IgE to Der p 1, 2, 5 and 7 were 10x, 5x, 2x and 4x greater than titres measures to Der f 1, 2, 5 and 7. The large differences especially for the major group 1 and 2 allergens show the value of using species-specific reagents and that studies conducted with reagents that do not use the allergens of the species in the environment will be spurious. Sera from Virginia USA, a region known to be infested with both species, had the same titres to allergens from both species.

IgE anti house dust mite antibodies in regions of scabies infestation

B. J. Hales, L. J. Pearce, L. A. Hazell, W. R. Thomas, T. K. Heinrich and W. Smith with S. F. Walton. Menzies Institute, Darwin

With increasing westernisation house dust mite allergy is becoming important in regions with lower socio-economic conditions. Many of these, such as some communities of Australian aboriginals, have had a large burden of infection with the scabies mite *Psoroptes scabiei*. Although distantly related scabies mites might produce allergens that induce IgE that cross-reacts with the house dust mite making diagnosis and epidemiological surveys difficult. A panel of purified house dust mite allergens was used to examine antibody binding in sera from people known to have had scabies exposure or crusted scabies. The IgE antibodies in these people typically had low titres to

the major house dust mite allergens Der p 1 and Der p 2 but were characterised by high titres to the group 4 and group 20 amylase and arginine kinase allergens. IgG antibodies reacted with a broader range of specificities but still with the highest titres to Der p 4 and 20. The Der p 20 allergen is a minor allergen for house dust mite allergy that only induced low titres so antibodies to this specificity can be used to identify responses to *S. scabiei*. It is also possible that the *S. scabiei* arginine kinase and amylase would be important antigen in the defence from scabies infections.

Recombinant and natural group 2 house dust mite allergens

W. R. Thomas, W. Smith, L. A. Hazell with S. Piboonpocanun and P. Vichyanond, Mahidol University, Bangkok

The group 2 house dust mite allergens can be readily produced as recombinant allergens that have high IgE binding activity and can be crystallized for X-ray crystallography. They are likely to be a forefront of initiatives to use recombinant allergens to improve the treatment and diagnosis of allergy. The structure of the recombinant polypeptide determined by X-ray crystallography and nuclear magnetic resonance is however different suggesting a conformational flexibility that could be required for the putative lipid binding activity. Structural comparison of different types of recombinant Der p 2 made by Dr Piboonpocanun with circular dichroism, intrinsic tryptophan fluorescence and binding of the hydrophobic probe ANS have shown differences in all the preparations. In particular that Der p 2 as secreted from the yeast *Pichia pastoris*, a eukaryotic host favoured for the production of allergens for human use, has little of the expected

secondary structure and no hydrophobic binding region. This was despite normal IgE binding activity. This not only provides information on the antigenic properties of the allergen but also demonstrates that structural measurements are required to authenticate recombinant allergens.

Cat allergens

W. Smith, S. E. O'Neil, L. A. Hazell, B. J. Hales, W. R. Thomas, T. K. Heinrich and S. Piboonpocanun, Mahidol University, Bangkok

The screening of cDNA libraries made from different tissues of the cat several cat allergens that might contribute to the development of allergic disease. This is especially relevant for people with rhinoconjunctivitis who have been found from studies of our own and other studies to have low IgE titres to the major allergen *Fel d 1*. Two of these allergens, breast and salivary expressed (BASE) protein and salivary lipocalin, are homologous to proteins found to be major allergen produced by other species. Ongoing studies are being conducted to produce structurally authenticated recombinant allergens for quantitative IgE binding studies and in case of cat haptoglobin, the isolation of the natural allergen from serum. A further sequence homologous to the major von Ebner gland lipocalins of dogs has been identified.

Sublingual desensitisation of allergic responses to cysteine protease antigens

P.T. Cunningham, C. E. Elliot and W. R. Thomas with P.G. Holt Cell Biology

A model of inhalation allergy to the cysteine protease

papain has been used to develop new desensitisation strategies relevant to the biochemically homologous Der p 1 allergen. The simple intranasal administration of papain induces persistent and boostable IgE antibody and sensitises for Th2 type lung inflammatory responses. Sublingual desensitisation of primed mice has been shown to inhibit the ability to induce further IgE antibody and the release of IL-5 into the serum after an inhalation challenge. The model has been further developed to show that the IgE and IL-5 responses induced by papain are largely dependent on the protease activity, the first demonstration of this in a non-adjuvanted system. Enzymatically activated papain was also more effective at desensitisation and where it was possible to inhibit the production of the Th2-associated chemokines TARC, MDC and TSLP as the lung inflammation. Similar desensitisation could also be achieved with the sublingual administration of papain absorbed to chitosan nanoparticles and with peptides containing the major T-cell epitope. These enhanced methods of sublingual immunotherapy are now being compared for their therapeutic efficacy against mixtures of allergens and anaphylactic responses.

A new source of anti-microbial peptides

T. K. Heinrich, T. L. Chai, A. Kutasi with P. M. Watt, Drug Development and G. R. Pocock, Microbial Dynamics.

Acinetobacter baumannii is an important cause of infection of debilitated patients such as burns victims and of hospital-acquired infection. It is of major concern because it has an intrinsic ability to develop antibiotic resistance and some isolates are resistant to all of the treatments mankind has available today. This bacterium is being used as a target to produce new types of peptide-based antibiotics. Most existing work on

peptide antibiotics for other microorganism has examined naturally occurring anti-microbial peptides or peptides based on their structural motifs. Here we have used a different strategy intended to produce a new range of peptides. A PCR based technique was used to produce 50-200 base pair random fragments from the genomes of a diverse range of bacterial and archaea and these were used to construct a phage display library in the lytic T7 bacteriophage. Phage enriched from the library by cycles of absorption and elution from the bacteria were screened for binding activity to the bacteria by ELISA and synthetic peptides were made to represent the peptide encoded by the positive phage. A number of structurally distinct peptides with anti-microbial activity in the low micromolar range have been identified and found to be active as proteolytic resistant retroinverso peptides, to have low toxicity for human cells and to appear to have varying modes of action.

Inflammation

Immunomodulatory effects of UVB radiation in mice

PH Hart, S Gorman, M Judge

UVB immunomodulatory effects have been implicated not only in skin cancer development but also in the initiation and progression of autoimmune and infectious diseases in experimental animals. UV rays cannot penetrate beyond the outermost layer of skin. In our studies, the effects of UVB on systemic immunomodulation are studied; the shaved dorsal skin of mice is irradiated whilst a second body site (for example the ventral skin, the peritoneal cavity or the respiratory tract) provides the site for antigen sensitisation several days later. The immunomodulatory effects of UVB result in reduced swelling of the ears when they are challenged by surface painting with the same antigen after a further five days.

They also result in reduced asthma-like responses to respiratory allergens. To better understand the molecular mechanisms involved, lymph node cells draining sites of UVB irradiation have been isolated and examined phenotypically and functionally. We now have evidence that UVB irradiation of mice on their shaved backs for a time equivalent to about 20 minutes in noon in summer in Perth causes an accumulation of regulatory T lymphocytes (CD4⁺CD25⁺FoxP3⁺) in the skin-draining lymph nodes and these regulatory cells can reduce subsequent immune responses in those nodes. We have continued to study the phenotype and function of these regulatory cells. Are new regulatory T cells induced or are we measuring an accumulation of regulatory T cells in the lymph nodes draining UV-irradiated skin? In addition, is the activity of cells increased? Many of these experiments have involved transfer of cells from a UVB-irradiated mouse into a naïve mouse subsequently challenged with antigen. There are many mechanisms by which regulatory cells can suppress immune responses. Many of these are being studied.

Funded by Cancer Council WA and NHMRC

Immunomodulatory effects of topical vitamin D3 application

S Gorman, M Judge, PH Hart, A Kuritzky

Upon irradiation with UVB, 7-dehydrocholesterol in skin converts to pre-vitamin D which then isomerises to vitamin D with body heat. Skin keratinocytes have an autonomous vitamin D pathway and can produce substantial amounts of 1,25 (OH)₂ vitamin D3, the hormonally active form of vitamin D3. We propose that any effects of vitamin D associated with acute UV exposure are dependent on 1,25 (OH)₂ vitamin D3 produced by keratinocytes and immune cells at the

irradiated site. Hence we are studying the effects of 1,25 (OH)₂ vitamin D3 applied directly to skin. Based on studies in human skin, local levels of 1,25 (OH)₂ vitamin D3 in the order of 2-5 nM can be achieved following erythematous UVB exposure. Using such levels painted onto skin, we have not detected increased numbers of CD4⁺CD25⁺FoxP3⁺ cells in draining lymph nodes but we have detected increased regulatory activity by these cells. Upon transfer to new mice, these T regulatory cells can suppress responses to several experimental antigens. In ongoing studies, the vitamin D3-activated T regulatory cells are being better phenotyped and further characterised and comparisons made with UVB-induced T regulatory cells.

Funded by Cancer Council WA and NHMRC

Effect of UVB on bone marrow-derived dendritic cells

PH Hart, J Lee, S Gorman, J Lisciandro, M Judge

In response to erythematous 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, and can replace those damaged by the inflammation. To our knowledge, there have been no studies of the phenotype and function of cells isolated from the bone marrow of UV-irradiated animals. Bone marrow cells were investigated following a single acute oedematous dose of UV. A comparison was made with the antigen presenting function of CD11c⁺ cells from the bone marrow of mice that had experienced a chemical hapten-initiated dermal inflammatory reaction. Dendritic cells derived from the bone marrow of mice exposed to acute inflammatory stimuli were significantly less efficient at presenting antigen to T cells both *in vitro*

and *in vivo*. This finding reflects a potential shift in our understanding of the immunomodulatory effects of erythematous UV irradiation of skin as we hypothesise that some of the systemic effects of erythematous/oedematous UV irradiation of skin may be a consequence of the inflammation induced in skin. These studies are important as skin inflammation may result in other ways such as from topically applied chemicals, infections or allergic responses.

Effect of UVB radiation and vitamin D3 on murine asthma models

PH Hart, JP McGlade, D Strickland, D Turner, S Gorman, J Lisciandro, A Kuritzky, M Judge

We have previously analysed the effect of UVB exposure on models of contact hypersensitivity, a response in mice dependent on type 1 or Th1 immune cells. The effect of a single exposure to UVB on two asthma models in mice has been examined, the expression of these responses being dependent on type 2 or Th2 immune cells. In the first model, mice were UVB-irradiated on their shaved backs three days before sensitisation, re-sensitisation and challenge intranasally with the cysteine protease, papain. In the second model, mice were irradiated on their shaved backs three days before sensitisation, and re-sensitisation, intraperitoneally with ovalbumin mixed with alum. The mice are subsequently challenged by aerosolised ovalbumin. Airways hyperreactivity was significantly reduced by exposure to UVB. The levels of inflammatory cytokines in lavage fluid, as well as antigen-specific responses by cells from the lung-draining lymph nodes, were reduced. 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. We have confirmed that a regulatory cell is induced by UV irradiation and can transfer the regulatory effects of UV into naïve mice. We are seeking the identity of these regulatory cells and their mechanism of action. In 2007 we also investigated the effect of UV irradiation and vitamin D3 on different routes of sensitisation to ovalbumin. Instead of intraperitoneal sensitisation with ovalbumin and alum, we investigated sensitisation to ovalbumin by application of skin patches containing the antigen alone. The contribution of UVB-induced vitamin D3 to these responses is also being assessed using models of both intraperitoneal and topical ovalbumin sensitisation.

Funded by NHMRC

Use of adenoviral vectors for dissection of cytokine mechanisms in activated human monocytes and macrophages

PH Hart, CM Prêl, E Woodward, J Bisley

Due to their phagocytic and poorly proliferative nature, it has been difficult to transfect human monocytes and macrophages isolated from human peripheral blood. This has been a stumbling block for use of primary monocytes and inflammatory macrophages for study of cytokine signalling pathways relevant to the development and resolution of inflammation. Adenoviral vectors have recently allowed transduction of a high percentage of human macrophages. We have now optimised this methodology using human monocytes isolated by elutriation from human blood kindly provided by the Perth Red Cross Blood Bank and an adenoviral vector encoding green fluorescent protein (AdV-GFP). We have been studying the mechanisms by

which monocytes/macrophages are activated and then how interleukin-4 (IL-4) and IL-10 suppress monocyte/macrophage inflammatory cytokine production. We have identified Suppressor of Cytokine Signalling-1 (SOCS-1) as a molecule rapidly induced by IL-4 in human monocytes. We hypothesised that SOCS-1 may be responsible for the ability of IL-4 to suppress pro-inflammatory mediator production by both human monocytes and synovial fluid macrophages. We have cloned the plasmid for SOCS1 into a pAdTrack-CMV vector. It was then recombined with the pAdEasy-1 vector in bacteria before infection of mammalian HEK-293 cells that allowed replication of the virus. After spinning the virus onto purified cells, we have confirmed expression of SOCS-1 in human monocytes and macrophages by Western blot. Overexpressed SOCS 1 regulated LPS activation. However, experiments investigating changes to signalling pathways do not suggest that SOCS-1 is part of the mechanism by which IL-4 is anti-inflammatory. Further, mechanisms by which IL-4 negatively regulates pro-inflammatory mediator production by human monocytes and macrophages may not be the same as those published for murine macrophages.

Funded by NHMRC

Staff and Students

Allergy and Immunology Group Research Staff

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

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Belinda Hales PhD

Tatjana Heinrich PhD

Wendy-Anne Smith PhD

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Keith Pearce BSc (Hons)

Tracey Chai BSc (Hons)

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Inflammation Group Research Staff

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Shelley Gorman BSc (Hons) PhD

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Melinda Judge BSc (Hons)

Joanne Liscandro BSc (Hons)

Jessica Lee BSc (Hons) until June 2007.

Postgraduate Students

Jacqueline McGlade BSc (Hons), PhD Candidate

Eleanor Woodward BSc (Hons), PhD Candidate

Jacqueline Bisley BSc, Hons Candidate

Visiting Student

Alexandra Kuritzky BSc (Hons), medical student from University of Toronto, until June 2007.

Awards

Prue Hart Appointed Adjunct Professor, University of WA. Reappointed NHMRC Principal Research Fellowship 2007-2011.

Shelley Gorman Richard Walter Gibbon Medical Research Fellowship, University of Western Australia, Faculty of Medicine and Dentistry, November 2007.

S. E. O'Neil Perron Meritorious Award

S. E. O'Neil University of Western Australia Convocation Travel Award

S. E. O'Neil Friends of the Institute Travel Award

Presentations

W. R. Thomas. Mining molecules in the mite. Workshop. European Academy of Allergy and Clinical immunology, Göteborg, Sweden

W. R. Thomas. Co-chair 4th International Workshop on indoor allergens and chronic allergic disease. Aspen, USA

W. R. Thomas. Cat Allergens. Australasian Society for Allergy and Clinical Immunology, Perth, WA

W. R. Thomas. IgE binding patterns in different populations. Symposium. World Allergy Organization Congress, Bangkok, Thailand

W. R. Thomas. Allergens and the immune system. Symposium. World Allergy Organization Congress, Bangkok, Thailand

W. R. Thomas. Trends in mite allergen research. Workshop. World Allergy Organization Congress, Bangkok, Thailand

B. J. Hales. Invited participant. 4th International Workshop on indoor allergens and chronic allergic disease. Aspen, USA

PH Hart Invited Symposium speaker and co-chair, European Society for Photobiology, Bath, UK, September 2007

PH Hart Invited Symposium Speaker, ComBio, Sydney, September 2007

PH Hart Invited Plenary Speaker, International Symposium: Effects of UV radiation on human health, and UV protection, Nara, Japan, November 2007.

S Gorman Regulatory T cell Keystone Symposium, Vancouver, Canada, February 2007.

S Gorman The Second Cancer Council Symposium, Perth, Australia, March 2007.

S Gorman Invited speaker, Australasian Society for Immunology, Perth, Australia, June, 2007.

S Gorman European Society for Photobiology, Bath, UK, September 2007.

S Gorman European Society for Dermatological Research, Zurich, Switzerland, September 2007.

S Gorman Mutagenesis and Experimental Pathology Society of Australia (MEPSA), Hobart, November 2007.

CM Prele, Invited speaker, Kennedy Institute of Rheumatology, Imperial College London, UK, June 2007.

CM Prele, 8th World congress on Inflammation, Copenhagen, Denmark, June 2007.

CM Prele, TLROZ 2007:Pattern Recognition Receptors in Immunity and Disease, Melbourne, Australia, May 2007.

JP McGlade, Mutagenesis and Experimental Pathology Society of Australia (MEPSA), Hobart, November 2007.

JP McGlade, Australasian Society for Immunology, Sydney, December 2007.

External Committees.

W. R. Thomas. NHMRC Program grants review panel

W. R. Thomas. International Allergen Nomenclature Committee

PH Hart Chair, NHMRC GRP 2e Inflammation.

PH Hart Member, Royal Perth Hospital Medical Research Foundation Scientific Committee.

CM Prele, S Gorman Members of the Organising Committee, ASMR Medical Research Week, June 2007.

Division of Population Sciences

Aboriginal Health Research

Advisory Council on the Prevention of Deaths in Children and Young People - Communicating the findings to Aboriginal communities

Dawn Bessarab, Roz Walker, Theresa Venz, Tracey-Lee Edwards, Marita Smith, Colleen Hayward

In May 2005 the Advisory Council on the Prevention of Deaths in Children and Young People (the Advisory Council) tabled in the WA State Parliament 'The First Research Report: Patterns and Trends in Mortality of WA Infants, Children and Young People' (Freemantle 2005). The Report details the all-cause and cause-specific mortality rates of infants, children and young people between 1980 and 2002 with particular focus on measuring the disparity in the patterns and trends of mortality between Aboriginal and non-Aboriginal infants, children and young people.

The Kulunga Research Network has been engaged to develop a communication and dissemination strategy, specifically targeted for the Indigenous community using the information from the First Research Report, as well as appropriate strategies for dealing with difficult issues linked to the Report.

The aim of the project is to conduct an Indigenous community education and dissemination project.

A three stage process will be undertaken over two years, plus an evaluation strategy.

Phase 1: Scoping Exercise -This first phase will involve further analysis of the report, collaboration to identify priority response areas, identifying existing communication initiatives and seek advice from people in the field.

Phase 2: Developing education materials - this phase will develop and implement innovative, culturally appropriate

materials in a relevant and understandable format that are linguistically appropriate for Aboriginal people from urban, rural and remote communities.

Phase 3: Communication and Dissemination Strategy

The aim of the strategy is to disseminate the findings through the implementation of the education materials. The aim is to:

- raise awareness;
- provide a better understanding of the issues;
- outline what specific action could be taken to address the issues in a preventative manner.

The dissemination will be conducted at 3 trial sites (metro, rural and remote).

The evaluation strategy will involve an in-depth evaluation at each of the developmental trial sites involving pre and post implementation tools through interviews and questionnaires and an assessment of the resource materials.

The project is funded by the WA Department for Child Protection with Kulunga being engaged by the project managers, the Advisory Council on the Prevention of Deaths of Children and Young People.

Cultural determinants of health and wellbeing in Aboriginal children and youth

Adele Cox

This is a Masters project to examine the association between cultural participation/cultural continuity and social and emotional wellbeing of Aboriginal Children and youth in WA, using the WA Aboriginal Child Health Survey (WAACHS) data and qualitative data to be

collected in the Kimberley region.

Funded by NHMRC (Program Grant)

Evaluation framework and research plan for the Building Healthy Communities (BHC) Onslow Leaping Lizards Project

Dr Roz Walker, Dr Clair Scrine, Mr Glenn Pearson

The long term project goal is to engage the Onslow community in implementing a self-directed and sustainable lifestyle program that empowers the community to aim for positive behaviours and holistic health in the short and long term. The primary aim of this proposal is to establish an Evaluation Framework to collect key baseline and qualitative data through which the Pilbara Division of General Practice (PDGP) can assess how effective the school based intervention is in enhancing child health and development by promoting community engagement by physical activities and recreation; and, improving community access to and understanding of the importance of nutrition; and reducing smoking and harmful alcohol consumption. The baseline data may include a survey of the current health status of all people living in the Onslow region, based on interviews, survey, Census and school data. The Evaluation Framework and baseline data will enable a greater assessment of the current status of health, and wellbeing of different population groups within the Onslow community. The Evaluation Framework developed will utilise both quantitative and qualitative research methodologies to identify participant satisfaction and project efficacy in contributing to the broader goals of the BHC as well as the key issues encountered by the Project Officer. Funded by Pilbara Division of General Practice

Evaluation of the Strong Women, Strong Babies, Strong Culture Program - Pilbara

Dr Clair Scrine, Mr Daniel McAullay

The proposed evaluation aims to obtain comprehensive, meaningful data about the impact of the SWSBSC program in 4 sites across the Pilbara region. The evaluation will assess whether there is an association between the SWSBSC program and improved indicators of maternal health and infant health, especially birth weight. Birth weight is commonly used as a measure of antenatal care and as a key indicator of the health status of the infant. Lower birth weight is associated with a higher risk of a number of chronic diseases in adult life and as such, a person's life expectancy. Research questions to explore will include: Has there been a change in the proportion of low birth weight babies (<2500gms) and Proportion of Optimal Birth Weight (<.85) of Aboriginal babies born in the Hedland area since the full implementation of the program. Has there been a change in the proportion of preterm births (<37 weeks gestation) of Aboriginal babies in the Hedland area since the full implementation of the program? Has there been a change in the rate of neonatal transfers to Perth of Aboriginal babies born in the Hedland area since the full implementation of the program?

Funded by St John of God Health Care

Impact of swimming pools on children's health in remote Aboriginal communities

Deborah Lehmann, Mary Tennant, Desiree Silva, Peter Jacoby, Jacinta Johnston, Jenny Smith, Kulunga Research Network, Fiona Stanley in collaboration with Helen Wright (Port Hedland Regional Hospital), Harvey Coates, Francis Lannigan (Princess Margaret Hospital), Sharon Weeks (Professional Hearing Services)

Swimming pools were built in four remote Aboriginal communities in Western Australia in 2000. A before-and-after study of children in two of these communities showed a reduction in burden of skin infections and otitis media.

We examined data collected at local clinics in Jigalong and Mugarinya to see if there has been any change in clinic attendance and antibiotic treatment since the pools were opened. We found a reduction in antibiotic prescription and in clinic attendance for middle ear infections, respiratory infections and skin infections. These findings will appear shortly in the Medical Journal of Australia.

This study is funded by the WA Department of Housing and Works

Indigenous Mental Health Textbook

Colleen Hayward, Roz Walker, Glenn Pearson, Michael Wright

The aim of this project is to develop a textbook on culturally appropriate approaches to assessment and interventions for Aboriginal and Torres Strait Islander social and emotional well being and mental health issues. The textbook is to be developed by clinicians, cultural and educational experts. The resource will have

applicability across Indigenous Australia. This project will:

- identify, commission and coordinate key Indigenous and non-Indigenous experts and stakeholders in the mental health sector to provide written contributions as appropriate; pilot-test; and
- develop the textbook and promotional materials to master copy stage.

The scope of the textbook is to include context relating to historical and present day social health and emotional wellbeing issues and the evolution of current Indigenous social and emotional wellbeing and mental health policy directions. It will incorporate specific clinical mental health assessment processes and culturally appropriate treatment interventions. An editor will need to be engaged to ensure that a quality, readable and publishable resource is produced.

The textbook will assist Vocational Education Training (VET) and Tertiary Education Training (TET) students and other key stakeholders to understand a variety of perspectives relating to social and emotional well being and mental health issues for Aboriginal and Torres Strait Islander people.

The project is funded by the Australian Government Department of Health and Ageing, with Kulunga being engaged by the project managers, the Australian Council for Educational Research (ACER)

Job aspirations for Indigenous young people in the East Kimberley

Dr Roz Walker, Clair Scrine

The aim of this project is to engage with Indigenous young people in the East Kimberley region to identify their aspirations, motivators, barriers and overall views toward employment, both locally and out of the region. The research team will identify and use the most appropriate processes to identify the barriers, supports, and stakeholder perspectives towards education and employment and to ascertain the employment aspirations of young Indigenous people in the East Kimberley region. Participants will be asked questions such as: * What does their future look like? * What do they see as possible in relation to work? * What opportunities do they see? * What could hold them back and why? The information gathered from the focus groups and individual interviews will be collated into strategic themes or categories, in accordance with the terms of reference.

Funded by Wunan Foundation Inc

Newborn Asthma and Parental Smoking (NAPS) project - Indigenous Women's project

Dr Roz Walker, Ms Karina Aiberti, Ms Tracey-Lee Edwards

The Newborn Asthma and Parental Smoking Project (NAPS) Project – Phase IV, was a 2 year, state-wide health promotion project (March 2005 – March 2007) managed by the Asthma Foundation of WA and funded by Healthway. Kulunga was committed to undertake part of the Indigenous component which looked at ways to promote the 'Care for my air!' message to Aboriginal women who are pregnant.

The aim of this project is to produce, trial and evaluate

a range of culturally appropriate resources to increase awareness among Indigenous women about the effect of passive smoking on the fetus and infant with a particular focus on asthma. As part of this overall objective a minimum of 50% of Aboriginal health workers (AHWs), and Aboriginal Liaison Officers (ALOs) working in metropolitan Perth and the Wheatbelt region will be engaged to participate in the project's information session. The resources produced will highlight the links between passive smoke exposure and development of childhood asthma. Kulunga will contribute to the distribution of these resources to AHWs and ALOs throughout the Perth and Wheatbelt regions for dissemination to Indigenous women.

The work of this project was sponsored by Healthway, with Kulunga being engaged by the project managers, the Asthma Foundation of WA.

Rio Tinto Child Health Partnership

Colleen Hayward, Clair Scrine, Tracey-Lee Edwards, Theresa Venz, Marita Smith

The Rio Tinto Child Health Partnership (the Partnership) is a collaborative mechanism designed to fast-track improvements in the health and wellbeing of Aboriginal and Torres Strait Islander children and families, proactively addressing Indigenous maternal and child health nationally.

The Partnership aims to deliver improvements in Aboriginal and Torres Strait Islander maternal and child health by:

- Providing an evidence base for future policy and decision-making, as well as service provision;
- Focusing on prevention and effective intervention and the development of tangible outcomes; and

- Advocating for collaborative political and community action and social change by gathering and making available key data and research.

These objectives are met through three projects:

- National policy and planning information for Indigenous child health, education and wellbeing;
- National Fetal Alcohol Spectrum Disorder prevention strategy; and
- National Indigenous community health workforce development strategy.

Funded by Rio Tinto Ltd, Alcohol Education and Rehabilitation Foundation, the governments of Western Australia, Queensland and the Northern Territory and the Office of Aboriginal and Torres Strait Islander Health (within the Australian Government Department of Health and Aging)

St. John of God Health Care Collaboration

Clair Scrine, Daniel McAulley

Under the St. John of God Health Care Collaboration, Kulunga was engaged to measure the effectiveness and impact of the Strong Women, Strong Babies, Strong Culture (SWSBSC) program in sites in the Pilbara. The SWSBSC program aims to increase infant birth weights and improve maternal weight status through earlier attendance for antenatal care.

The evaluation found there is widespread support for the program and that the continuity of care and commitment of staff involved in the delivery of the program is significant. Recommendations to strengthen and enhance the program covered the capacity building of staff, the implementation of consistent data collection

and reporting mechanisms, increased training on a range of issues, increased resources and improved communication processes. This collaboration is sponsored by St. John of God Health Care Inc. It is part of an ongoing relationship anticipated to run over a five year period.

WAACHS - Western Australian Aboriginal Child Health Survey

Dr David Lawrence, Mr Francis Mitrou, Prof Steve Zubrick, Prof Sven Silburn

The project is to analyse and subsequently incorporate the results of the WAACHS into three remaining volumes and to oversight a communication dissemination strategy to convey research results to stakeholders. In total, five volumes of WAACHS research will be published. Volume 1: The Health of Aboriginal Children and Young People was launched on 3 June 2004. Volume 2: The Social and Emotional Wellbeing of Aboriginal Children and Young People was launched on 13 April 2005. The launch of the remaining three volumes will occur within the life of this project and a final report on project outcomes will be provided to the Office for Aboriginal and Torres Strait Islander Health (OATSIH) three months after the launch of Volume 4. The working titles for the remaining three WAACHS publications are: Volume 3: Aboriginal Education, health and Well Being Volume 4: Aboriginal Family and Community Volume 5: Aboriginal Health, Education and the Juvenile Justice System.

Funded by Commonwealth Office of Aboriginal and Torres Strait Island Health Services

Whole of Government Strategic Framework for Indigenous Generational Change

Colleen Hayward, Mr Glenn Pearson, Mr Carrington Shepherd, Dr Roz Walker

Evidence clearly highlights the continuing disparities between Indigenous and non-Indigenous people in terms of life expectancy, infant deaths, preventable diseases, and education and employment outcomes. A drastic shift in how we respond to the needs of the Indigenous population is urgently needed if this unacceptable situation is to change. This highlights the need for a comprehensive whole-of-government and community policy Framework that addresses the particular needs of Indigenous people in Western Australia.

The proposed framework draws on the findings of the WA Aboriginal Child Health Survey and the available literature on child and human development interventions, and is consistent with the Council of Australian Governments (COAG) Overcoming Indigenous Disadvantage framework

The WA Department of Indigenous Affairs is facilitating the development of the Strategic Framework and an associated Blueprint for Action.

Australian Early Development Index

Australian Early Development Index (AEDI)

Sven Silburn, Sally Brinkman, Sharon Goldfeld, Frank Oberklaid, Mary Sayers.

The Australian Early Development Index (AEDI) is the Australian adaptation of the Early Development Index (EDI) used in other countries, most notably in Canada. It represents an innovative approach to understanding

child development in Australia. For the first time, communities have access to local data about children's development to inform their early childhood policies and enable them to plan and organise their community-based services for young children and their families.

The AEDI provides communities with a tool to focus attention on how young children are doing, and gives data that can serve as the impetus for community mobilisation and capacity building around early childhood. The AEDI is designed to also assist communities to monitor and evaluate early childhood programs and interventions.

The support of the TICHHR is required to inform the development of the national AEDI implementation. Issues such as assessing the measurement of change in AEDI scores at a jurisdictional and national level, facilitating the national rollout at a State and Federal level, training local communities and agencies in the use and action around the AEDI results are some examples of the support expected.

Funded by Department of Education, Employment and Workplace Relations – Australian Government

Starting on Track: The Pilbara AEDI Initiative

Colleen Hayward, Roz Walker, Carrington Shepherd

The Starting on Track project involves the implementation of the AEDI in the areas of Hedland and Newman. The project is undertaken in partnership with BHP Billiton Iron Ore and forms part of the BHP Billiton Iron Ore's commitment to health in the Pilbara region. It aims to:

Use the AEDI to provide baseline data on the strengths and vulnerabilities of pre-primary age children in the

Hedland and Newman areas; and

Provide training and support to communities to plan, identify and implement local and region-wide strategies and interventions to improve the development outcomes for young children.

Following BHP Billiton Iron Ore foundation and principal support, the AEDI was applied to all Pilbara sites with a pre-primary enrolment. With 100% participation, this was the first time a region of this extensive size had wholly participated in the AEDI.

Funded by BHP Billiton Iron Ore

Development of an Indigenous Australian Early Development Index (IAEDI) :To develop, pilot and evaluate a culturally appropriate version of the Australian Early Development Index (I-AEDI) for use with Indigenous children.

Prof Sven Silburn, Colleen Hayward, Roz Walker, Carrington Shepherd

The primary aim of the project is to undertake the field work and analysis necessary for developing an adaptable and appropriate version of the Australian Early Development Index (AEDI) for use with Aboriginal children. The project will determine the factors required for an instrument for national application that is inclusive of Aboriginal perspectives of children's readiness to learn at school and is able to demonstrate a measure impact for Aboriginal children in the five domain areas identified in the AEDI - social competence, physical health and wellbeing, emotional maturity, language and cognition, and community skills and general knowledge. At the conclusion of the three years it is expected that either a new stand-alone instrument will be developed

for use with Indigenous communities, or that the existing AEDI will be modified or a supplement developed for use in an Indigenous context. The project also aims to build community capacity in the selected regions by transferring research skills through the training and employment of local people in the project, communicating information about effectiveness of local services and resources through targeted workshops and seminars, empowering Aboriginal communities through access to high quality local data and research findings relevant to the development of children and facilitating access to Commonwealth and State funding through existing State and Commonwealth programs.

Funded by Shell Australia, Department of Families, Community Services and Indigenous Affairs (Australian Government)

Staying on Track: Substance Reduction Program for Aboriginal Young People in Port Hedland and Newman Expanding the Australian Early Development Index (AEDI) into the Port Hedland and Newman areas

Colleen Hayward, Roz Walker, Carrington Shepherd, Sven Silburn

BHP Billiton, through its Health Partnership Agreement with the WA State Government has invited the Institute and Kulunga to initiate a number of projects that target activity in identified areas of need within the Greater Pilbara Region. Kulunga through the WAACHS findings for this region indicates a significantly young Aboriginal population with reported high levels of alcohol (27%), tobacco (11%) and marijuana (24%). There was also reported levels of mental health problems within the Region. It was agreed with BHP that a substance reduction program targeting Aboriginal young people in this region

and specifically the Port Hedland and Newman areas should be designed, trialed and evaluated to address this issue. BHP has also asked that Kulunga apply for matching funding and or in-kind support for the project. The in-kind support has been clearly matched by the projects access to the WAACHS findings and a funding submission has been presented to the Pilbara Resource Commission's Pilbara Fund. A Memorandum of Understanding (MOU) between BHP and the Institute has been prepared to confirm arrangements for funding for this and the AEDI project. Both these projects will be managed through Kulunga.
BHP Billiton

Birth defects and Developmental Disorders

Alcohol and Pregnancy: Aboriginal women's knowledge, attitudes and practice

Ms Heather D'Antoine, Professor Nadine Henley, Ms Jan Payne, Professor Elizabeth Elliott, Professor Carol Bower, Professor Anne Bartu

Our research objective is to obtain information from Aboriginal women from two regions in Western Australia (WA), the Kimberley and the Goldfields, about alcohol consumption in pregnancy using qualitative methodology. A similar project will be conducted in the metropolitan area but is not the subject of this application. This study will provide information to inform policy and practice and guide health promotion initiatives aimed at preventing alcohol exposure in pregnancy and Fetal Alcohol Spectrum Disorder (FASD).

Alcohol and Pregnancy: Health promotion for health professionals

Ms Jan Payne, Professor Carol Bower, Professor Elizabeth Elliott, Professor Nadine Henley, Mrs Colleen O'Leary, Ms Heather D'Antoine, Professor Anne Bartu

Associate Investigators Ms Lynda Blum, Ms Roslyn Giglia, Dr Janet Hammill, Ass Pro Ray James, Dr Christine, effries-Stokes, Dr Anne Mahony, Mr Daniel McAullay, Ms Anne McKenzie

The Alcohol and Pregnancy Project builds on our previous research where health professionals reported their need for resources such as written materials for themselves and for distribution to clients.

The aim of the project is to increase the proportion of WA health professionals who provide routinely ask and advise women about alcohol use during pregnancy and its consequences.

In 2006, we synthesised international and national literature and resources. This synthesis provided the evidence-base for the content of the Alcohol and Pregnancy resources. Issues relating to the communication of information on alcohol use during pregnancy were explored through focus groups and interviews with health professionals (Aboriginal health workers, nurses, allied health professionals, general practitioners, obstetricians and paediatricians) in metropolitan Perth and country areas. We also gathered qualitative data from Aboriginal and non-Aboriginal women of child-bearing age about the communication of alcohol consumption during pregnancy and its effects.

This evidence-based information and qualitative data from WA health professionals and women shaped the development of the *Alcohol and Pregnancy: Health Professionals Making a Difference* information pack.

The information pack contained four resources, a comprehensive booklet and a fact-sheet for health professionals, wallet cards for health professionals to hand to women after they have asked and advised them about alcohol use during pregnancy, and a desk calendar.

The *Alcohol and Pregnancy: Health Professionals Making a Difference* information pack was distributed to over 3,500 health professionals in WA in 2007. These evidence-based health promotion resources will support health professionals' knowledge and advice to pregnant women and women of child-bearing age about alcohol use during pregnancy.

The evaluation of the resources commenced in October 2007 when over 1,900 health professionals in WA were surveyed about their knowledge, attitudes and practice regarding alcohol and pregnancy and whether the resources had changed their practice or their intentions to change their practice. These data will be analysed in 2008.

Funded by Healthway Project Grant #15177 2006-2008, and the NHMRC Program Grant #353514 2005-2009

Alcohol and Pregnancy: Women's knowledge, attitudes and practice

Ms Jan Payne, Professor Carol Bower, Professor Elizabeth Elliott, Professor Nadine Henley, Mrs Colleen O'Leary, Ms Heather D'Antoine, Professor Anne Bartu; Associate Investigators Ms Lynda Blum

The Alcohol and Pregnancy: Women's knowledge, attitudes and practice project describes Western Australian (WA) women's knowledge, attitudes and

practice regarding alcohol use in pregnancy. A computer assisted telephone interview was used to collect data from a random, representative sample of 500 WA women aged 18 to 45 years on their knowledge, attitudes and practice regarding alcohol use in pregnancy and Fetal Alcohol Spectrum Disorder. A third of the women were not aware of the consequences on the fetus and child of drinking alcohol in pregnancy and a quarter of them would continue to drink alcohol in a future pregnancy. The majority of women agreed that information about the effects on the fetus of alcohol and pregnancy should be available to women and that health professionals should ask women about alcohol consumption and advise them to abstain during pregnancy. These results will be used for future health promotion programs for women. This project is funded by the Healthway Project Grant #16163 2006-2007, and the NHMRC Program Grant #353514 2005-2009

Alcohol and Pregnancy: Survey of Western Australian Women

Ms Jan Payne, Dr Elizabeth Peadon, Professor Carol Bower, Professor Elizabeth Elliott, Professor Nadine Henley, Mrs Colleen O'Leary, Ms Heather D'Antoine, Professor Anne Bartu

The objective of this research is to obtain information from WA women aged from 18-45 years who are not pregnant to:

- Assess their knowledge, attitudes and practice regarding alcohol use in pregnancy following the distribution of best practice health promotion resources for health professionals and workforce development and capacity building activities;

- obtain base-line data on women's knowledge, attitudes and practice before proceeding to inform women about the effects of alcohol use in pregnancy using mass media; and
- assist in the design and development of the future mass media campaign to inform women of childbearing age about the effects of alcohol consumption in pregnancy.

Specifically, we will measure their:

- Knowledge of the effects of alcohol consumption in pregnancy on the fetus and child; *sources of information about the effects of alcohol consumption in pregnancy;
- knowledge of the NHMRC guideline regarding alcohol consumption in pregnancy;
- attitudes to alcohol consumption in pregnancy;
- practice (or practice intentions) regarding alcohol consumption in pregnancy; and *support for initiatives to provide women of childbearing age with information about the risk of alcohol consumption in pregnancy.

Funded by NHMRC Program Grant #353514 2005-2009

[Alcohol in pregnancy: Health outcomes and use of hospital services by children of mothers with a recorded alcohol-related condition](#)

O'Leary C, Bower C, Geelhoed E, D'Antoine H, Bartu A.

Parental alcohol misuse impacts negatively on the child in one of two ways, each of which has a very separate aetiology. Children can be exposed to alcohol

misuse during (either or both periods): - the antenatal period - the research studies have focused on maternal alcohol consumption patterns; - during childhood due to chronic parent alcohol misuse - the research studies predominantly focus on paternal alcohol consumption. Benefits: There are limited data on the rate of hospitalisations, health outcomes, and costs associated with children whose mother has a diagnosis of an alcohol-related condition recorded during pregnancy and no Australian data have been published to date. The information contained with provide researchers and health and family services to develop appropriate programs which will address the needs of this high-risk group of children and their mothers. Overview: Hospital morbidity data will be obtained from the Data Linkage Unit (DLU) on all women admitted to hospitalised with an alcohol-related condition and who were identified as pregnant between July 1999 and December 2004 (approx n=500) and linked with the Midwives' data, Mental Health Information System, Birth Defects Register, Cerebral Palsy Register, the Intellectual Disability Exploring Answers (IDEA) database, Drug and Alcohol Service data and death data.

Awaiting data linkage which should be completed mid-2008.

Funded by NHMRC Program Grant

[Alcohol in pregnancy: The impact of low to moderate maternal alcohol consumption on child outcomes](#)

Mrs Colleen O'Leary, Bower C.

Co-authors of fetal growth paper are Colleen O'Leary, Carol Bower, Natasha Nassar and Jenny Kurinczuk

Co-authors of language delay paper are Colleen O'Leary, Carol Bower Steve Zubrick, Kate Taylor, and Glenys Dixon

The aim of the study is to determine the health and developmental outcomes and use of health services by the offspring of women who have consumed alcohol during pregnancy compared with the outcomes for children not exposed to alcohol in-utero.

Research has commenced on the RASCALS (Randomly Ascertained Sample of Children in Australia's Largest State) data and two studies have been undertaken to date. Investigations of the relationship between maternal alcohol consumption during pregnancy and the impact on the developing child have included:

1. Impact of maternal alcohol consumption on fetal growth and preterm birth; This paper has been completed and is under review February 2008.
2. Prenatal Alcohol Exposure and Language Delay in Two-Year Old Children: The importance of dose and timing on risk; This paper has been completed and is under review February 2008.

A study investigating child development in 2 year old children will be undertaken in the first half of 2008.

Funded by NHMRC Program Grant

Epidemiology of hypospadias in Western Australia

Nassar N, Bower C, Barker A (PMH)

This project involves a number of studies investigating the incidence and trends, risk factors and health outcomes associated with hypospadias in Western Australia (WA). Hypospadias is a urogenital birth defect occurring in infant boys and is the second most common birth defect in WA.

The first study investigating hypospadias involved the examination of the prevalence and trends of hypospadias in WA between 1980 and 2000. Findings showed a total of 1788 cases were registered during the study period with hypospadias diagnosed on average for one in every 285 births. Results also highlighted that the rate of hypospadias increased by 2% per annum from 28 per 10,000 births in 1980 to 43 per 10,000 births in 2000 and, in particular, the rate of moderate or severe hypospadias (which occurs in 11% of all cases) almost doubled. There was also a consistent rise both in infants diagnosed with isolated hypospadias and infants who also had other co-existing anomalies, although infants with co-existing anomalies were more likely to have a severe form of hypospadias. The results from this study have been accepted for publication in the Archives of Disease in Childhood.

Studies currently underway include an investigation of maternal and paternal reproductive health and genetic risk factors that may be associated with hypospadias; and another study to investigate the health status, outcomes and health service utilisation of infants with hypospadias and those who have had surgical repair in WA between 1980 and 2003. A further study is also being conducted in collaboration with investigators from the Children's Hospital Boston to determine the association between first trimester maternal serum

levels of human chorionic gonadotropin and the risk of hypospadias or other urogenital anomalies.

Funded by NHMRC Public Health Postdoctoral Fellowship

Investigation of Pharmaceutical Benefits Scheme medicines prescribed in pregnancy

Colvin L, Bower C, Slack-Smith L

The medicine data recorded under the Pharmaceutical Benefits Scheme (PBS) will provide a rich resource of epidemiological research at the population level. At present in Australia, surveillance of adverse effects of prescribed medicines upon the fetus does not adequately exist. This study will provide the basis for a novel surveillance of pregnancy outcomes in Australia by linking the PBS data for each pregnant woman to hospital admissions and to birth, death, hospital admission and possibly WA Birth Defects Registry data for the child. The specific objectives of the project are: 1. to determine the internal and external validity of the PBS dataset with respect to pregnant women using existing reports of medicine use (the 2001 National Health Survey by the Australian Bureau of Statistics (ABS); published Australian studies); 2. to describe PBS medicines prescribed to pregnant women in WA, in terms of sociodemographic characteristics of the women, trimester, by drug classification, and by the Australian 'categorisation of risk of drug use in pregnancy'; 3. to explore applications of the PBS data for maternal and child health research in WA through linkage with other population-based datasets available in the WADLS; for example, the Midwives' Notification System (MNS) and the WA Birth Defects Registry (BDR). Pregnancy outcomes such as gestational age,

birthweight, Apgas scores, birth defects, mortality (stillbirth and neonatal death) and multiple births will be included.

Funded by Australian Postgraduate Award (APA) scholarship

Significant adverse health outcomes in children born following assisted conception treatment

Hansen M, Petterson B, Bower C, Colvin L, Kurinczuk J, De Klerk N, Leonard H, Webb S.

Adverse perinatal outcomes are more common in singletons born following Assisted Reproductive Technology (ART) and this would predict an increase in hospitalization during infancy and early childhood. We investigated hospital admissions during the first three years of life for all singleton children born in Western Australia between 1994 and 2000 (1328 ART, 162,350 spontaneously conceived (SC)). We found that ART infants were more likely to be admitted to a neonatal intensive care unit, to be hospitalized in the first year of life and to stay in hospital longer than spontaneously conceived children. Couples undertaking ART should be aware they are more likely to have a preterm, low birth weight baby who is more likely to be hospitalized and to stay in hospital longer than other children.

We are currently analysing birth defects data for all ART children born in WA between 1994 and 2002.

Funded by NHMRC Project Grant and Supplementary Postgraduate Scholarship - Friends of ICHR

Intellectual Disability

[Leaving School: Maximizing participation and life outcomes in youth with an intellectual disability transitioning from secondary school to adult life.](#)

Leonard H, Bower C, Bourke J, Dyke P

This project seeks to explore the challenges faced and outcomes achieved by students with an intellectual disability as they move from secondary school into adult life. The study will form a collaboration of a broad range of stakeholders working in the area around Australia, including researchers, families, service providers and policy makers in the areas of education and training, disability, therapy, recreation and employment.

This project was funded by a Seeding Grant received from ARACY supporting a new collaboration on this topic. The aim of the project was to explore the challenges faced and outcomes achieved by students with an intellectual disability as they move from secondary school into adult life. In comparison to non-disabled youth, the transition of adolescents with an intellectual disability is characterised by wider scope, longer duration and attenuated experiences.

A workshop was held in November 2007 to bring together from around Australia a broad range of stakeholders working in the area. Researchers, families, service providers and policy makers in the areas of education and training, disability, therapy, recreation and employment attended the two day workshop. The ultimate outcome of the two days of information exchange was the collaborative agreement to produce a research grant application addressing key issues related to the topic. This grant application will aim to investigate the factors at an individual, family, and societal level which positively and adversely affect outcomes for young people

with an intellectual disability as they move into adulthood and their family (as measured by participation, wellbeing and quality of life of young people and their families). The International Classification of Functioning, Disability and Health (ICF) will be used as a framework.

Funded by Australian Research Alliance for Children and Youth (ARACY)

[Validation of the instrument of perceived effect of child disability on siblings and parents.](#)

Young D, Li J, Nesse M, Aberteri K

The purpose of this research is to develop and trial a set of three instruments (adult, adolescent and child forms) for measuring the effect of disability on siblings, parents and carers of children with a disability (autism or intellectual disability). We already have an instrument for use with adolescent siblings of children with an intellectual disability, but it has not been fully trialed. This project will validate these three instruments using psychometric methods and it will provide the basis for a large scale study on child intellectual disability. Importantly, the validation will be based upon both qualitative and quantitative methodology.

Funded by UWA Research Grants Scheme

Rett syndrome

[Developing clinical guidelines for the management of scoliosis in patients with Rett syndrome](#)

Scoliosis is a common orthopaedic complication that affects girls with Rett syndrome and develops in approximately 75% of girls with Rett syndrome by 13 years of age. There is limited literature of management

strategies for scoliosis in Rett syndrome and it is difficult to accumulate clinical experience. A study using the expertise of clinicians and parents to develop a set of clinical guidelines for the management of scoliosis in Rett syndrome is now nearing completion. The initial stages of this project were managed by Anke Bergmann as in part completion of her Master of Science degree at Curtin University of Technology.

An initial set of practice statements and questions were based on the literature, evaluation of the experiences and concerns of parents and the clinical experience of the researchers. A modified Delphi technique was then used to further develop this initial document. To this end, an international and multidisciplinary panel of clinicians and parents were recruited. Panel members then participated in a multistage review process responding to statements and questions in password-protected online documents. Review of practice statements was based on a pre-determined level of consensus. The final document contained practice points relating to awareness of the potential for scoliosis in all girls with Rett syndrome, monitoring, conservative management of scoliosis and peri-operative management.

We are currently collating endorsements of the panel members for the guidelines document and will then disseminate the findings via publication and parent and professional associations. We also plan to assess the reach of the dissemination process in an Australian context.

[International: InterRett](#)

Leonard H, Fyfe S, De Klerk N, Anderson A, Bebbington A, McHugh M, Carter P

During 2007 the AussieRett group continued to manage the international phenotype database InterRett, which

has funding from the International Rett Syndrome Foundation (IRSF) until December 2009. InterRett collects data from families and clinicians around the world through online and paper based questionnaires. The database currently contains over 1200 cases from over 30 different countries. These large case numbers provide researchers with the opportunity to investigate subgroups of individuals who share the same mutation and compare their phenotype with each other and against groups with different mutation types. An investigation of this nature using InterRett data was published in *Neurology* in March 2008. 2007 honours student, Sandra Louise, provided a descriptive analysis of the sociodemographic, clinical and genetic characteristics of the subject in the InterRett cohort. These were then compared with the Australian population-based cohort and the results will be included in a publication focussing on the strengths and weaknesses of this resource.

Funded by International Rett Syndrome Foundation

National - Rett syndrome: determinants of outcome and burden (AussieRett)

Leonard H; Bower C; de Klerk N; Silburn S; Christodoulou J; Ellaway C; Fyfe S; Hall S; Msall M; Nagarajan L; Reilly S; Woodhead H; Ravine D

AussieRett, as the Australian Rett Syndrome Study is now known, is a population-based study following 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 years. Information is collected at each questionnaire on the person'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. Since Rett syndrome is a movement disorder an extremely important and innovative source of study data is video footage provided by the subjects' families. During 2007 families provided a second round of the video material to the study.

The study has a multi-disciplinary investigative team which includes input from psychologists, physiotherapists and speech therapists 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 Johns Hopkins University, Professor Alan Percy from the University of Alabama and Professor Michael Msall from the University of Chicago.

Analytical investigations using data relating to different aspects of the study continue to be undertaken and during 2007 seven articles relating to the study were published. The work covered a range of topics from specific medical problems associated with Rett syndrome such as epilepsy and sleep problems to complex aspects of the genetics. We have also been

able to report on the process of collection and coding of the video material that has occurred over the last few years. We also studied the overlap between autism and Rett syndrome and compared those who were and were not considered to have autism prior to the diagnosis of Rett syndrome. Genetic studies included an investigation of the influence of X-chromosome inactivation on clinical severity in subjects with the two commonest *MECP2* (Rett syndrome genetic) mutations.

UWA Research Grants Scheme 2007: Feasibility of measuring occupational exposure in a rare disorder using the Internet) a pilot project

Leonard H, de Klerk N, Fritshi L, Anderson A, McHugh M

During 2007 a group of families from the International Rett syndrome study InterRett were invited to participate in an online pilot study. The main objective of the study was to trial an online tool developed to collect information on job history and job specific details. This information can be used to assess possible workplace exposure to toxic agents. The trial is in its final stage and is proving to be successful from both a participant and research perspective.

Down syndrome

Down Syndrome (NOW) Study (Down Syndrome NOW Study Report)

Leonard H, Bower C, de Klerk N, Silburn S, Fyfe S, Hall S, Msall M, Bourke J, Dyke P, Jacoby P, Hogan D, Maley A

The aim of the Down Syndrome NOW study is to collect information about a range of issues facing children and young adults with Down Syndrome and

their families and provide valuable information to current and future parents, medical professionals, educational institutions and service providers. A grant from the Disability Services Commission was received in 2006 to produce a report to be distributed to parents and service providers on the findings in the study.

This report, published in October 2007, translates the information collected through the Down syndrome NOW study from over 350 families throughout WA with a child with Down syndrome. It reflects the current needs and status of these children and young adults and their families. The report includes information on the child's medical issues, functional abilities and social relationships; family demographics and the health of parents; and information on therapy, medical and respite services accessed by families.

Further analysis of the data has investigated the physical and mental health of the mothers and found the most important predictors of maternal health were children's behavioural difficulties, everyday functioning and current health status. Mothers of children with Down syndrome appear to experience poorer mental health and may require greater support and services to improve behaviour management skills for their child and their own psychological well-being.

Funded by Disability Services Commission

Capacity building in Population and Indigenous Health

Community Participation in Population Health research

Anne McKenzie

Consumer and community participation initiatives and activities continued to grow throughout the Institute in

2007. Within the Division of Population Sciences there has been a significant uptake of the ideology of consumer and community participation in many and varied ways. This has included:

The formation of new community reference groups for research areas such as the Infectious Diseases Research Group and the Child Development Study.

Conducting training sessions for staff, PhD students and consumer representatives involved in the Developmental Pathways in WA Children Project.

Facilitation of focus groups with parents who participated in the Down Syndrome NOW Study to seek input into the issues they wanted highlighted in the final report of the study.

The continuing development of existing reference groups such as the Raine Study Youth Group (Teen Team), the Alcohol and Pregnancy community reference groups and the Aussie Rett parents group.

A significant increase in planned and funded consumer and community participation activities in grant applications.

The inclusion of consumer and community participation in the strategic planning activities for the Division.

Increased collaborations and networking opportunities between the community and researchers within the Division.

The Capacity Building Grant, which finished in October 2007, enabled the establishment of many consumer and community participation activities. It is anticipated that the foundations laid during this period, will continue to grow with the mainstreaming of the role of the Consumer Research Liaison Officer from core funding.

Not Just Scholars But Leaders: Learning Circles in Indigenous Health Research

Jason Barrow undertook a leadership role through his position as project Coordinator

Hayward C, Lehmann D, Stanley FJ, Eades S, de Klerk N, Gilles M, Gray D, Larson A, Slack-Smith L, Thompson and C Watson C; Bessarab D, Brown N, J Coffin, Hammill J, Jones J, Kickett-Tucker C, McAullay D, Milroy H, Wilkes ET and Wright M

The Indigenous Capacity Building Grant (ICGB) "Not Just Scholars but Leaders: Learning Circles in Indigenous Health Research" is a collaborative project that has its prime objectives:

- Building the capacity of Indigenous health researchers
- Population health research outputs and achievements
- Evidence of research into practice, links to policy, dissemination.

The researchers on this project are called Team Investigators. During the life of the grant, they will develop and enhance their skills in research around four major themes:

- Commitment to Indigenous communities;
- Health services research;
- Lifestyle, behaviour and susceptibility to disease; and
- Pathways to resilience and wellbeing.

The ICGB crosses the jurisdictions of Western Australia, the Northern Territory and Queensland by virtue of the location of the Aboriginal researchers supported by the grant

Funders of the project: The ICGB is primarily funded by the National Health and Medical Research Council (NHMRC) with support funding from Curtin University of Technology for the five year life of the grant, 2005 – 2009

In addition to the funding partnership the ICGB brings together the Telethon Institute for Child Health Research (TICHR), the University of Western Australia (UWA) and the Combined Universities Centre for Rural Health (CURCH)

Childhood cancer

Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children

Milne E, Bower C, de Klerk N, Kees U, in collaboration with Armstrong B, van Bockxmeer F, Baker D, Fritschi L, Thompson J, Lockwood L, Rice M, Stevens M, Smbert E, Suppiah R, Alvaro F, Downie P, Haber M, Norris M, Scott R, Attia J, Marshall G, Miller M.

Researchers in the Childhood Cancer Epidemiology program have now completed the final year of a five-year (2003-2007) NHMRC funded national case-control study into the causes of childhood acute lymphoblastic leukaemia (ALL). The primary hypothesis of this study is that maternal folate supplementation during pregnancy protects against ALL in the offspring, with the effect modified by genetic factors in folate metabolism. This study addresses the actions and interactions of supplemental and dietary folate, environmental exposures, and genetic polymorphisms in parents and children in determining the risk of childhood ALL. The team is multidisciplinary, bringing together molecular biologists, geneticists, oncologists and epidemiologists. Case subjects comprised children (0-14

years) newly diagnosed with ALL in Australia between 2003 and 2006. They were identified through all the paediatric oncology centres in Australia. Two controls were selected for each case, frequency matched by age, gender and State of residence. Controls were identified using random digit dialing. Data collection instruments were specifically developed for use in the study: self administered exposure questionnaires for each parent and food frequency questionnaires for the mother (during pregnancy and breastfeeding), the father (in the 12 months prior to the pregnancy), the child's current diet (completed by the parent) and their diet as an infant. Telephone follow-up interviews asked about occupational and other exposures. An occupational exposure expert, blinded to case/control status, is examining all the occupational information and will allocate probability and amount of exposure to the chemicals with reference to a custom designed database of jobs and exposures. Blood and buccal samples were taken from the case child (in remission), and blood samples were taken from his/her parents. Recruitment and data collection are now complete. In total, we were notified of 519 eligible cases and 484 (93%) of these were invited to participate in the study. Of these 416 (80%) gave consent, 66 declined (14%), and 2 died prior to consent. Completed questionnaires were received from a total of 387 case families (93%) and 870 control families (64%). DNA was collected from 415 case children (100%) and 539 control children (51% of those asked). Data cleaning and preparation for analysis of the final datasets is well under way. Initial analyses should be complete by mid 2008. Funded by NHMRC.

National Case-Control Study of the Causes of Childhood Brain Tumours

Milne E, Bower C, de Klerk N, Dallas P, in collaboration with Armstrong BK, van Bockxmeer F, Baker D, Fritschi L, Thompson J, Hassall T, Kirby M, Kellie S, Ashley D, Pinkerton R, Alvaro F, Ashton L, Norris M, Scott R, Attia J, Cohn R, Miller M

The Australian Study of Childhood Brain Tumours (AUS-CBT) is a national, NHMRC funded, case-control study 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). Researchers in the Childhood Cancer Epidemiology program have now completed the second year of AUS-CBT, and in 2007 the NHMRC gave approval for the recruitment period of the study to be extended to 2010.

Cases are children aged 0-14 diagnosed with a CBT at one of the 9 paediatric oncology units in Australia, and their parents. The study involves retrospective recruitment of cases diagnosed in 2005 as well as prospective recruitment of cases diagnosed in 2006 onwards. In total, 276 eligible cases from 2005-2007 have been notified to us. To date, 217 (79%) of eligible cases have been invited to participate, 148 (54%) have consented and 46 (17%) families have declined to participate. 26 (9%) cases will not be invited by the treating oncologist for medical or psychosocial reasons. We are liaising with the clinicians regarding inviting and consenting the remaining 56 (20%) eligible cases.

Controls are children aged 0-14 who have not been diagnosed with a CBT, and their parents. They are identified using random digit dialing and are frequency matched to cases by age, gender and State of residence.

AUS-ALL controls will be used for cases diagnosed in 2005 and 2006. AUS-CBT control recruitment commenced in 2007 and so far 87 (63%) families have given their consent to participate in the study.

Data collection for both cases and controls is progressing well and instruments include self-administered exposure questionnaires for each parent and food frequency questionnaires for the mother, father and child. Telephone follow-up inter views ask about occupational and other exposures. DNA (blood or buccal) samples are also being collected from the child and parents for genotype analysis, which will commence in 2008.

Funded by NHMRC.

Population Based (WA) Data Linkage Study Of The Relationship Between Intra-Uterine Growth and Childhood Cancer.

Milne E, Bower C , de Klerk NH, Blair E, Laurvick C

This study uses population-based linked health data to investigate the relationship between birth weight and risk of cancer in children. The primary analysis of the relationship between intra-uterine growth and risk of ALL is complete and a paper describing the results was published in the American Journal of Epidemiology (Vol 166, No.2). The results showed a linear relationship between 'proportion of optimum birth weight' and risk of ALL, particularly in younger children. This finding indicates that risk of ALL is not related to birth weight per se (as previously reported), as the relationship was also observed in children who did not meet any definition of 'high birth weight'. This question has not been previously investigated.

The group next investigated whether the observed

association extends to other types of childhood cancer and to siblings of the index children. A paper on central nervous system (CNS) tumors and lymphomas has been accepted for publication in the International Journal of Cancer. The results showed that the risk of Hodgkin and Burkitt lymphoma increased with increasing fetal growth among boys only, whereas the increased risk observed with non-Hodgkin lymphoma was only in girls. As in the ALL paper, these associations with fetal growth were also observed among children not classified as high birth weight, suggesting that accelerated growth is more important than birth weight per se. The results were similar when cases were compared with their unaffected siblings, suggesting that the increased growth associated with cancer risk was not general to the family. No relationship was observed between fetal growth and risk of CNS tumors.

Funded by NHMRC.

Trends in Childhood Cancer in Western Australia 1960-2005

Milne E, Laurvick C, de Klerk N, in collaboration with Thompson J (WA Cancer Registry)

This study uses population-based linked health data to investigate whether the incidence of childhood cancers has increased in Western Australia over the last 30 or 40 years. The results to date indicate that there may have been an increase in the incidence of acute lymphoblastic leukemia of 3-4% per year since 1982 among girls and children aged 5-14 years. These results were also supported by national Australian data. Other studies are continuing.

Child nutrition and development

Dietary factors and trajectories of mental health from infancy to adolescence

Wendy H. Oddy, Therese A. O'Sullivan, Monique Robinson, Garth E. Kendall, Margaret Miller M, Peter Jacoby, Nick de Klerk, Sven R. Silburn

Nutritional risk factors for mental health morbidity from infancy to adolescence are being identified and their associations with cognitive and emotional development are being described. We are examining the extent to which mental health morbidity may be attributable to specific nutritional factors such as breakfast eating, omega-3 fatty acid intake and dietary patterns and how these might mediate and/or moderate other psycho-social risk factors. Our paper titled A good quality breakfast is associated with better mental health in adolescence has been submitted to the Journal of Adolescent Health

Funded by NHMRC Program Grant.

Nutrition and mental health: Fatty Acids and Depression Project

Wendy H. Oddy, Sven Silburn, Steve Zubrick, Therese O'Sullivan, Trevor Mori, Lawrie Beilin

Dr Wendy Oddy has been invited to present work from this study in September 2008 at the Brain Phospholipids conference, Oslo, Norway.

Dr Trevor Mori in the School of Medicine and Pharmacology coordinated the red blood cell analysis for fatty acids and these results are currently being analysed in association with mental health outcomes.

The Growth & Development Study

Dr Susan Byrne, Dr Eve Blair, E Davis, Tim Jones, N McLean, Prof Sven Silburn, Prof Steve Zubrick

The primary aim of the study is to identify the biopsychosocial factors, and their causal pathways that contribute to the development and persistence of childhood obesity, so that these pathways may be targeted in prevention programs. The study involves three groups of children (a community sample of overweight/obese children, a community sample of healthy weight children, and a treatment-seeking sample of obese children) and their parents. A comprehensive assessment protocol is used to assess a broad range of factors (biological, psychological and social/environmental) that may influence the development and persistence of childhood obesity. Children and their parent(s) are assessed, separately, immediately upon enrolment into the study, and then at six-monthly intervals for at least three years. This design will enable both longitudinal and cross-sectional data to be examined. Assessments include the collection of height and weight data, and measures of a broad range of biological, psychological and social/environmental factors that are purported to influence the persistence of childhood obesity into adolescence and adulthood

Funded by Western Australian Health Promotion Foundation (Healthway)

The influence of fitness and body mass index on cardiovascular risk in children

Dr Katie Watts, Dr Susan Byrne, E Davis

A project within the Childhood Growth and Development Study, this research will investigate the

influence of cardio respiratory fitness and body mass index on cardiovascular co-morbidities in children.

Funded by National Heart Foundation

Measuring pre- and postnatal growth

Blair E, deKlerk N, Lawrence D, Pereira-Gale J

This project aims to obtain better measurements of the appropriateness of growth using routinely available data, so that they may be on total population data. It has created the proportion of optimal measures of weight, length, head circumference and weight for length at birth. These are now being used in many TICHR projects. Biacromial diameter is being measured in the 16 year follow up for Raine study participants, to investigate whether this measure of skeletal size can improve the value of weight for height measures in children.

Databases and Information Technology for Population Studies

Cerebral Palsy Register (WA)

Watson L, Blair E, de Groot J, Stanley F

Cerebral palsy (CP) is a chronic neurological condition affecting movement and posture, ranging in severity from barely noticeable to severely disabling. As there is no cure, prevention and effective management are top priorities. The longstanding WA CP Register is used to monitor the occurrence of CP in WA and carry out research to investigate its causes and evaluate treatment strategies.

Cerebral Palsy Register (Australian) (ACPR)

Blair E, Watson L, de Groot J, F Stanley and the ACPR national collaboration

Our lack of knowledge regarding the extent and distribution of CP across Australia, and the need for larger sample sizes in order to investigate sub-types of CP, led to the setting up of a national collaboration to combine CP data from all States and Territories. Coverage of the national live birth population has increased from 45% at the outset to almost 100% in 2006, with only the Northern Territory still seeking funding. An internet website donated to the NSW CP Register by Macquarie Bank and Accenture, further developed and maintained as a donation by Paul Novak of Compots, provides all States with facilities for data entry, management and transfer, also making it possible for the public to directly contribute data. The Australian Cerebral Palsy Register (ACPR) was co-ordinated by WA CP Register staff from its inception in 2002 until 2007 when the administrative centre was moved to.

Analysis of case control study of term and preterm cerebral palsy WA 1980-95

Ms Jan de Groot, Dr Eve Blair

The primary aim is to prevent the occurrence of brain damage responsible for cerebral palsy in Western Australia by identifying points on each causal pathway to cerebral palsy where they may most effectively, efficiently and ethically be interrupted. In order to achieve this we must 2. Identify the details of causal pathways currently responsible for cerebral palsy in Australia.

CP Foundation (2006-8)

Developmental Pathways in WA Children Project

Stanley, F., de Klerk, N., Bower, C., Li, J., Ferrante, A., Leonard, H., Kendall, G., Price, P., Smith, M., Mathews, R., Jessop, M., Lander, F., Patterson, Y., Chalmers, R., and Freemantle, J.

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 Department of Health, Department of Education and Training, Department for Child Protection, Department of Corrective Services, Department of the Attorney General, Disability Services Commission, and the Office for Youth. The project has established the process of linking together longitudinal, population-based data collected and stored by each of the WA government departments and the Telethon Institute for Child Health Research, to create a fantastic cost-effective research and policy planning/evaluation resource.

Currently the linked data is being used by researchers and the respective departments to identify multi-level and early determinants of developmental outcomes and the interrelationships among them. It is anticipated that 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 encourage cross-agency collaboration, to ensure improved health, well-being and development of children and youth, their families and their communities.

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. 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 an ARC Linkage Project Grant.

Subprojects within the Project

A multi-level approach to childhood literacy and numeracy: Developmental pathways and the role of early health

Conducted by Eva Malacova (PhD Candidate)

Supervised by Dr Jianghong Li, Assoc Prof Eve Blair, Prof Nick de Klerk and Dr Helen Leonard

This research seeks to identify the key factors (at the individual, family and area level) that lead either to good or to poor literacy and numeracy skills, and how their impact differs across socioeconomic strata (as defined by SEIFA). In addition, this research aims to determine factors which mediate the socioeconomic disadvantage of area and parental socioeconomic disadvantage on educational outcomes.

“Towards prevention – A population health approach to child abuse and neglect: A measurement model and the identification of antecedent causal pathways”

Conducted by Melissa O'Donnell (PhD Candidate)

Supervised by Prof Fiona Stanley, Dr Helen Leonard, Ms Natasha Nassar, Ms Yvonne Patterson and Mr Richard Mathews

This project uses longitudinal population data from the Western Australian Government Departments of Child Protection, Health, and Education which has been linked and de-identified through the Data Linkage Unit at the Department of Health. This administrative data will be used to: develop a population measure of abuse and neglect independent of Child Protection Services data, to enable the monitoring of population trends in abuse and neglect; compare proportion of cases obtained on the measure to the Department of Community Development care and protection data, and describe the physical, psychological and social characteristics of abused and/or neglected cases, families and community of residence.

“Changing socioeconomic inequalities in neonate, infant and child health and development”

Conducted by Amanda Langridge (PhD Candidate)

Supervised by Dr Sunalene Devadason, Dr Jianghong Li, Prof Stephen Zubrick and Dr Jim Codde

This project will use longitudinal, administrative data from the Western Australian Government Departments of Health, Education and Child Protection to compare over time the socioeconomic inequalities in child health and developmental outcomes in Western Australia children and youth. It is anticipated these findings will determine which child, family, and area level indicators should routinely be collected to best inform Government policies and practices that seek to minimise these inequalities.

“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 area”

Conducted by Glenn Pearson (Masters Candidate)

Supervised by Assoc Prof Jane Freemantle, Dr David

Vicary and Prof Sven Silburn

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”

Conducted by Anna Ferrante (PhD Candidate)

Supervised by Dr Frank Morgan, Dr David Indermaur, Prof Stephen Zubrick and Dr Hilde Tubex

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: developing a profile of the risk and protective factors to support a strategy for change”

Conducted by Jocelyn Jones (PhD Candidate)

Supervised by Assoc Prof Jane Freemantle, Assoc Prof Maria Harries and Dr Kathryn Trees

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.

“A population-based, record-linkage study to elucidate the effects of child maltreatment on developmental pathways to mental health, suicidal behavior and suicide”

Conducted by Kristine Northey

Supervised by Dr Jianghong Li, Prof Sven Silburn, Dr David Lawrence and Mr Richard Mathews

This project will use whole population data available through the Western Australian Data Linkage System to investigate the extent to which childhood maltreatment contributes to the subsequent childhood and adult risk for mental health problems, deliberate self-harm and suicide.

IDEA - Intellectual disability exploring answers

Prof. Carol Bower, Dr Helen Leonard, Jenny Bourke

IDEA Advisory Council 2006: J. Bourke, C. Bower, H. Leonard (TICHR), B. Petterson, J. Valentine (PMH), V. Morgan (UWA), R. Sanders (Dept of Education and Training), A. Mathews (DSC), K. Stopher (DSC), P. Chauvel (Consultant), P. Rowe (SCDC), C. Rook (Consumer)

Changes to the protocol in 2006 have resulted in delays in the process of updating the IDEA database, which receives annual notifications of children identified with an intellectual disability from the Department of Education and the Disability Services Commission. These are linked by the Western Australian Data Linkage Unit to each other and to all current

notifications on the database.

Although no new linked data from Disability Services Commission (DSC) and Education have been received in 2007, further improvement of records currently in the database has occurred through use of medical information manually entered from forms.

Studies investigating early causal pathways of mental health problems and the impact of low to moderate maternal alcohol consumption during pregnancy on child outcomes have received IDEA data in 2007. Approval to access the database has also been given for a study measuring the burden of genetic disease in the WA population.

In 2007, a study on the association between intrauterine growth and subsequent intellectual disability (ID) in the child found the odds of mild-moderate and severe ID among Caucasian children was over two times greater for infants who experienced severe growth restriction (percent of optimal birth weight, POBW<75), and was similar for Aboriginal children. Infants with excess fetal growth (POBW>124%) were found to have a greater tendency of ID, especially autism spectrum disorders (ASD), particularly for males and term births. Severe growth restriction and poor head growth were independently associated with increased odds for severe ID.

Another study using data from IDEA and other linked databases has examined the trend of ASD over time in Western Australia and the possible effects and contribution of diagnostic substitution, changes in diagnostic criteria, age at diagnosis and eligibility for service provision based on ASD diagnoses.

Funded by Disability Services Commission.

Maternal and Child Health Research Database

Cosgrove P, Berinson M, Ball S, Good G, Nguyen H

The Maternal and Child Health Database is a linked database of maternal and childhood population data that remains an important data resource within the division and a key component of various collaborations with other external groups and researchers.

The record linkage collaboration with the Data Linkage Branch (DLU) at the WA Department of Health continues. The collaboration involves record linkage work previously done at ICHR being carried out at the DLU. It also involves a contribution by ICHR of resources to the DLU linkage program and the provision of an annual de-identified snapshot of linked health data being provided by the WA Department of Health to the Institute. The DLU system and linked data resources are governed by best practice privacy sensitive protocols that have been developed in WA and are designed to optimize linkage efficiency with minimum risk for individual privacy. The collaboration is working well, with feedback from ICHR researchers helping the Data Linkage Unit to continue to ensure the high quality of their linkage data. The Maternal and Child Health Database currently contains linked health records for all children born in WA between 1980 and 2003 and an update to include data for births between 1980 and 2006 is pending. This data has been supplemented with data from the Australian Bureau of Statistics. Procedures have been put in place to determine and store additional information often required by researchers, such as which hospital admissions belong to a single episode of care. Work is continuing on the development of in-house web based computer applications for use in the area of metadata management and knowledge management. Metadata is 'data about data' and these systems are designed to allow data in

the Maternal and Child Health Research Database to be used as efficiently as possible, giving researchers easy access to associated key information on datasets and also to a knowledge base containing contributions by other researchers using these important data resources.

Studies of hospital morbidity, and the association between morbidity and mortality in WA Indigenous and non-Indigenous infants, children and young people

Freemantle CJ, Read AW, DeKlerk NH, Officer K, Alpers K, Woods M, Cosgrove P, Anderson IP (University of Melbourne), Stanley FJ.

Work has continued on the database with data now being collected for the years 2004 and 2005. Data for the year 2006 have also started to be collected. We have now nearly a quarter of a century of comprehensive mortality information that describes the deaths of Western Australian born infants, children and young people. The data include information describing the environment of sudden and unexpected deaths, the circumstances of the deaths, forensic toxicology, the nature of deaths due to accident and injury, location of the deaths, the pathology of infections that lead to death and a number of other variables of interest, particularly for deaths believed to be preventable. Funding for the review of the deaths, the classification, coding and validation of the cause of death and the analysis of the data, had been obtained.

One of the main aims of the continuing development of this database is the ability to provide comprehensive information that will enable the development of targeted policy and evidence based initiatives that will prevent deaths among WA infant, children and young people. The data will also provide the baseline data from which to evaluate the effect of interventions and policy

development and implementation. The data also provide the base from which to consider the patterns and trends among the Aboriginal and non-Aboriginal populations over a quarter of a century. The data continue to provide this valuable information to support the development of government policy, community strategy and identification of areas of critical need. The WA Department of Health award for 'Healthy Partnerships' for the work undertaken in preventing Sudden Infant Death Syndrome (SIDS) in Aboriginal communities demonstrates the value and importance not only of the data but the application of the data to assist in preventing deaths in WA infants. Furthermore, this award recognises the importance of knowledge exchange and building strong collaborations with Aboriginal communities and health professionals.

These data are also being analysed to describe the comparative infant mortality in Australian Aboriginal, Alaskan Native and Maori infants. These analyses will be the first of their kind and have resulted from continuing collaborations with colleagues in Alaska and New Zealand.

Funded by Health Promotion Research Fellowship

Teleforms Equipment

Prof Nicholas de Klerk, Prof Fiona Stanley, Prof Steve Zubrick

Teleform enables the quick and easy capture and conversion of paper-based and electronic forms into digital data. However, the technique requires very specific expertise and equipment. Currently, the availability of such a service is limited in Perth, WA. We are only aware of a single reliable company that carries out this service - Savant. This draws high consultancy costs which impacts on funding, and also raises major issues of data

confidentiality and security in sending forms off-site for scanning. Sending the development of forms off-site also reduces the readiness of activating changes to forms for immediate deployment to printing and does not support ad hoc printing of customised questionnaires (customised with ID numbers or dates of return etc). We believe that Teleforms not only enables the above but also facilitates the development of aesthetic questionnaires/forms. The ability to print questionnaires in high definition colour would impact highly on the attractiveness of questionnaires to our project participants. As indicated, high optical definition printing and high optical resolution scanning are critical features of successful optical character recognition.

The Teleforms software purchased by the group in 2006 for use in questionnaire development and processing, continues to be used by projects within the Division. This computer software and accompanying computer hardware facilitates the streamlining of the data collection process by studies at the Institute that collect data using questionnaires.

Funded by NHMRC: Equipment Grants

The Western Australian Twin Register

Janice Hansen, Phyllis Alessandri, Nick de Klerk, Lyle Palmer, Jessica Lee.

The WA Twin Register (WATR) was established in 1997 using a grant from the WA Health Promotion Foundation (Healthway), and initially comprised data on all WA multiple births between 1980 and 1992 inclusive. The main purpose for establishing the Register was to invite families to participate in the WA Twin Child Health (WATCH) study which examined the roles that genes and the environment play in the link

between childhood asthma and atopy, and exposure to environmental tobacco smoke. The Register has since been extended to include 1993-1997 births, using funding from the National Health and Medical Research Council (NHMRC), and, more recently, 1998-2006 births using funds from the Australian Twin Registry NHMRC Enabling Grant. A total of 17,941 multiple birth children, born in WA between 1980 and 2006 inclusive, have been identified, representing 2.5% of all births during that time. They comprised 8,596 sets of twins, 241 sets of triplets, quadruplets and quintuplets. Seventy-six families had two sets of multiples during the time period. The WATR is the only population-based register of multiples in Australia, and one of only a few anywhere in the world. Adult twins born in WA between 1974-79 have also been approached by a team from the Centre for Genetic Epidemiology at WAIMR to enrol on the Register.

A number of studies have used data from the WATR including WATCH, WATCH for Asthma, Indoor Air Quality, Looking at Language, MZ twins discordant for ADHD, and the relationship between immune functions and asthma and allergy.

Funded by NHMRC.

The WA Twin Child Health (WATCH) study.

Janice Hansen, Phyllis Alessandri, Nick de Klerk.

The aim of the WATCH study was to collect data from families of multiples born in WA between 1980 and 1992 who belonged to the WA Twin Register, to examine the roles that genes and the environment play in the link between childhood asthma and atopy, and exposure to environmental tobacco smoke. Over 90% of eligible families of multiples have been contacted

and invited to join the WATCH study. Completed questionnaires have been received from nearly 2,500 families (57%), resulting in data from over 13,000 individuals.

In WA twin families, the prevalence of asthma was higher in children than in their parents (27.0% vs. 15%). Mothers had a higher rate than fathers (18% vs. 12%), but in children, girls had a lower rate than boys (24% vs. 30%). In children aged 6-12 years, the prevalence of asthma was higher in boys than girls (34% vs. 24%), but there was no difference in the prevalence in children aged 13-18 years (25% vs. 25%). There was no difference in asthma prevalence between twins and their siblings (28% vs. 26%), and between monozygotic (MZ) and same-sex dizygotic (DZ) twins (28% vs. 27%). Risk of asthma in twins was increased six-fold if both parents were asthmatic. Other factors which increased the risk of asthma in twins included being male, living in the city, having no older siblings, mothers experiencing a threatened miscarriage during pregnancy, having at least one episode of otitis media during childhood, having had tonsils removed, and being in the bottom 10% with respect to the SEIFA indexes of disadvantage and economic resources. There was no relationship between asthma in twins and exposure to environmental tobacco smoke (ETS).

Compared with DZ twins, MZ twins had a significantly higher concordance (76% vs. 49%, respectively) and correlation (87% vs. 48%, respectively) for asthma, resulting in an estimate of heritability at 78%. For twin data, variance components analysis showed that only additive genetic effects were important, and that shared environment effects were not significantly related to the risk of asthma. For twin family data, analysis showed that additive genetic effects and either genetic dominance or shared sibling environment were important, and

that shared family environment appeared to play no part in the risk of asthma. New statistical methods have been developed to analyze twin-family data which allow one critical assumption of the classic twin method that is, that the environments of MZ and DZ twins are equal, to be tested directly. These methods have been described and tested by Janice Hansen, Study Coordinator, who was awarded her PhD on the WA Twin Register and Asthma in twin families.

WA Family Connections Genealogical Database

Emma Glasson, Nick de Klerk

The WA Family Connections Genealogical Project is only one of three population-based genealogy registers in existence. The project consists of a system of electronic links that represent genealogical relationships for individuals living in Western Australia (WA). The relationships are defined from information recorded on birth, death and marriage registrations as well as other data sources used for data linkage activities at the WA Data Linkage Branch. The data exist as a supplementary system of links to the WA Data Linkage System and are managed using the same best-practice privacy protocols and data linkage procedures. The project is intended to facilitate health research with a focus on the inheritance of disease. The information can be used to assess the degree of relatedness of individuals within study samples, assist in locating common ancestors and allow estimates of genetic risk. Phase 1 of the project uses information recorded on electronic birth registrations that are available since 1974 and electronic death and marriage registrations available since 1984 (approximately 1.3 million records). Phase 2 will create genealogical relationships from birth, death and marriage registrations that are currently only available as paper records, with an

initial focus on the 0.9 million records that date back to 1950.

WA Register for Autism Spectrum Disorders

Glenys Dixon, Emma Glasson, Sarah MacDermott, Carol Bower, John Wray

Autism spectrum disorders include autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). They are characterised clinically by significant impairment in social interaction and communication, and by a restricted or repetitive range of interests. Symptoms may be apparent before 30 months of age, but diagnosis is tentative before this time. Many children have difficulties integrating into society and each require varying degrees of supervision and support in daily living. Our current understanding of the aetiology and intervention strategies for autism spectrum disorders is limited. The WA Autism Register serves as a primary resource to researchers, clinicians and service providers to provide knowledge of the diagnostic patterns of these complex disorders.

Since January 1999, the WA Register for Autism Spectrum Disorders has collected demographic and diagnostic information on newly diagnosed cases in WA. Annual summaries are made of the number and ages of people diagnosed, the severity of their disability, and some biological, diagnostic and developmental features. To date, the Register has collected information for more than 2000 children, adolescents and some adults who were newly diagnosed with an autism spectrum disorder. After nine years of operation, the data are currently being used to calculate diagnostic prevalence rates for the WA population.

Infectious disease

An effectiveness study of pneumococcal polysaccharide vaccine among children in the highlands of Papua New Guinea

Deborah Lehmann, Nick de Klerk, Marty Firth in collaboration with Michael P Alpers (Centre for International Health, Curtin University of Technology)

In the 1980s pneumococcal polysaccharide vaccine was found to be efficacious in reducing mortality and severe morbidity due to acute lower respiratory infection when given from the age of 6 months onwards to young children in the highlands of Papua New Guinea. An effectiveness study of a 23-valent pneumococcal polysaccharide vaccine was subsequently undertaken between 1991 and 1995 when the vaccine was offered to all children aged 8-23 months attending rural child health clinics. The effectiveness of this vaccine in reducing mortality and hospitalisation for pneumonia is being evaluated.

This study is funded by the World Health Organization; NHMRC, as part of NHMRC Program Grant number 353514

Early weaning, smoking, stress and resilience among young Aboriginal women

Fiona Nichols, Annette Stokes, Jacinta Johnston, Ruth Monck, Christine Jeffries-Stokes, Deborah Lehmann in collaboration with Nguyntju Tjitji Pirni Inc, Bega Garribirringu Health Services Aboriginal Corporation

This largely qualitative project, a subset of ICHR's Kalgoorlie Otitis Media Research Project, investigated maternal smoking and breastfeeding patterns and characteristics; and Aboriginal perceptions of related

social determinants and appropriate interventions. Results were drawn from both our cohort study (100 Aboriginal and 180 non-Aboriginal mothers) and from qualitative data collected during interviews with 55 Aboriginal women.

Results indicated that, in line with national figures, smoking was common among both Aboriginal and non-Aboriginal mothers—with higher rates in the Aboriginal population. Infant feeding patterns indicated that exclusive breastfeeding among Aboriginal mothers was below national and international targets. Maternal smoking and infant feeding characteristics indicated that different factors may influence the decisions of Aboriginal and non-Aboriginal mothers regarding these behaviours. Study findings pointed consistently to stress (and by way of stress-response, to freedom-seeking behaviour) as a pervasive component in the lives of many Aboriginal people and as a central social determinant of early weaning and smoking behaviour. Related interventions should therefore include strategies to address stress-related causes. Local proposals included multi-faceted young mothers' support, activity and education centres. Some of these activities are already underway. A manuscript documenting our findings has been submitted for publication.

Funded by Healthway

Enhanced Surveillance of Invasive Pneumococcal Disease through the Vaccine Impact Surveillance Network

Deborah Lehmann, Hannah Moore, Judith Willis, Catherine Harrison, Cherie Higgins, Michele Caneppele, Leanne Brown in collaboration with Tony Keil (Department of Microbiology, Princess Margaret Hospital), Denise Murphy (Public Health Bacteriology Laboratory, Brisbane), Peter Richmond (School of Paediatrics and Child Health, University of Western Australia), Carolien Giele (WA Department of Health) for the VISN Network

The Vaccine Impact Surveillance Network (VISN) was established in 1996 to collect and analyse information pertaining to vaccine-preventable diseases and assess the impact of vaccination programs specific to these diseases. Invasive Pneumococcal Disease (IPD) is a disease caused by *Streptococcus pneumoniae* (pneumococcus) invading a normally sterile site such as blood and cerebrospinal fluid. IPD is a major cause of pneumonia, septicaemia, bacteraemia and meningitis worldwide, primarily affecting young children and the elderly. Within Australia, incidence rates of the disease across all ages are particularly high in Aboriginal people.

Although IPD only became a notifiable disease in 2001, VISN has collected epidemiological and microbiological data on all reported Western Australian IPD cases since 1996. This has been facilitated via review of hospital records and reporting from Public Health and Infection Control Units

A 23-valent pneumococcal polysaccharide vaccine (Pneumovax) has been recommended since 1986 for Aboriginal adults aged 50 years or more, for younger Aboriginal adults with known risk factors and for non-Aboriginal Australians aged 65 years or more; since

2005 Pneumovax has been fully funded by the Federal Government. The 7 valent pneumococcal conjugate vaccine (Prevenar) was licensed in Australia in 2001 and since then has been available to Indigenous children and others at high risk of disease at no cost. In January 2005 it became available to all Australian children at no cost to parents.

During 2007, updating and cleaning of all data has continued, with the bulk of the work largely complete. Up to December 31st 2007 there were a total of 1913 episodes of IPD recorded on the VISN database over a period of nearly 12 years. In 2007 there were 123 reported cases of IPD and 22 deaths (18% case fatality rate); this compares with 131 cases and 11 deaths (9% fatality rate) in 2006. There were 26 cases of IPD in children aged less than 5 years in 2007 compared with 18 in 2006. In Aboriginal children there were 3 cases (IR = 37/100 000) of IPD in 2007, a reduction from 6 cases (75/100 000) in 2006. In contrast, there was an increase in non-Aboriginal children from 12 cases (incidence rate = 10/100 000) in 2006 to 23 cases (incidence rate = 20/100 000) in 2007. While 33% (n=4) of IPD cases in non-Aboriginal children aged under 5 years were due to serotype 19A (which is not included in Prevenar) in 2006, 43% (n=10) were due to this serotype in 2007. IPD incidence in Aboriginal adults aged 30-< 50 years also warrants close monitoring since rates have increased from 66/100 000 in 1996-2000 to 104/100 000 in 2006-2007. Much of the disease in Aboriginal adults is due to serotypes covered by Pneumovax. The changing epidemiology of IPD may be the result of one or more of the following: epidemics of non-vaccine serotypes, replacement disease by serotypes not include in Prevenar, limited uptake of Pneumovax and changes in surveillance practices.

In 2007, we presented IPD trends over one decade at several national conferences as well as an Indigenous immunisation research workshop. A comprehensive annual report for 2006 was widely distributed and we are preparing a manuscript for publication.

From January 2008 all IPD surveillance will be undertaken by the Communicable Disease Control Directorate (CDCD) at the WA Department of Health, while the team at ICHR will complete all data collection and cleaning for 1996 -2007. We have held discussions with CDCD regarding a study aimed at monitoring upper respiratory tract pneumococcal carriage in Aboriginal adults and children in several metropolitan and rural/remote areas of Western Australia. This will assist in predicting changes in circulating pneumococcal serotypes and monitoring patterns of antibiotic resistance.

WA Department of Health through the Collaboration for Applied Research and Evaluation

Impact of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea

Deborah Lehmann, Nick de Klerk, Marty Firth in collaboration with Michael P Alpers (Centre for International Health, Curtin University of Technology)

Following a report of increased risk of death associated with diphtheria tetanus pertussis (DTP) and oral polio vaccination of children living in rural areas of Guinea-Bissau, the World Health Organization Department of Vaccines and Biologicals sought proposals to determine the effects of routine infant immunisation on survival in areas of high mortality. We investigated the impact of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. Continuous monthly demographic surveillance enabled

us to identify births, deaths, migrations, and immunisation status of all children born in Tari between 1989 and 1994. The study determined the effect of DTP, BCG and measles vaccinations on mortality in the first two years of life and found no deleterious effects of infant immunisations. Our findings have been published in an international journal.

There has also been an investigation into some statistical methodology issues concerning longitudinal and observational data sets such as this one. A paper comparing the potential impact of the varying assumptions that different studies have made around the world is in preparation.

Funded by World Health Organization; NHMRC, as part of NHMRC Program Grant number 353514

Epidemiology of acute lower respiratory infections

Deborah Lehmann, Hannah Moore, Nick de Klerk, Peter Jacoby, Heather D'Antoine, Daniel McAullay in collaboration with Peter Richmond (School of Paediatrics and Child Health, University of Western Australia), David Smith (Division of Microbiology and Infectious Diseases, PathWest Laboratory Medicine WA), Tony Keil, Katie Lindsay (PathWest Laboratory Medicine WA, Princess Margaret Hospital)

The primary objective of this project, which is the subject of a PhD project, is to describe the aetiology, burden and causal pathways of acute lower respiratory infections in Aboriginal and non-Aboriginal children from a 10-year birth cohort using population linked data. This large data linkage project will involve linkage between hospital morbidity data, emergency department data, state-wide laboratory data, cerebral palsy register data, birth defects register data and data from births, deaths and midwives' notifications and when available, immunisation data from

the Australian Childhood Immunisation Register. In 2007, negotiations with various data custodians continued and have resulted in a Memorandum of Understanding between WA Department of Health and PathWest Laboratory Medicine WA for the extraction and linkage of state-wide laboratory data. The first release of linked data containing information from births, midwives' notifications, deaths and hospital admissions for acute lower respiratory infections is expected to be received in early 2008. The study will provide the essential baseline data on which to identify, recommend and evaluate appropriate preventive measures for acute lower respiratory infections in Aboriginal and non-Aboriginal children in WA.

As preliminary work for this project and as part of a Quality Activity Proposal approved by the Princess Margaret Hospital (PMH) Pathology Committee in December 2006 to investigate seasonal and temporal trends of respiratory viruses, de-identified data on specimens collected between 1997 and 2005 that were sent to the Department of Microbiology at PMH, were received in early 2007. Extensive data cleaning and analysis was the focus for 2007. We have identified respiratory syncytial virus (RSV), influenza A and B, parainfluenza types 1, 2 and 3 and respiratory adenovirus as the major viruses routinely identified through cell culture and direct immunofluorescence. While identification rates are similar between Aboriginal and non-Aboriginal children, the median age at the time of identification is significantly lower for Aboriginal children than non-Aboriginal children for all viruses except RSV. All viruses exhibit distinct seasonality and influenza shows different seasonality for Aboriginal and non-Aboriginal children: in Aboriginal children influenza identifications peaked in May and September, whereas in non-Aboriginal children identifications showed a single peak in August. The seasonality of RSV and adenovirus differs with

age. This work will help identify target groups for future immunisation programs and other appropriate interventions. A manuscript is now in preparation and this work was presented at several national conferences in 2007 including an Indigenous Immunisation Workshop in Darwin and the WA Branch of the Public Health Association of Australia.

Funded by NHMRC, as part of NHMRC Program Grant number 353514, Theme 4: Infection

Establishment of an Infectious Diseases Community Reference Group

Deborah Lehmann, Hannah Moore, Kirsten Alpers, Anne McKenzie

In 2007 we commenced planning for 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. Terms of Reference were drafted and were presented along with a brief introduction to infectious diseases research at ICHR's Consumer and Community Advisory Council.

Funded by NHMRC/Wellcome International

Collaborative Research Grant 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 (Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea) and Peter Richmond (School of Paediatrics and Child Health, University of Western Australia)

Throughout the world an estimated one million children die annually from pneumococcal disease, the majority in early infancy. This study is designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in 300 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 PCV 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 will also assess 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. Ms Jacinta Francis from the Papua New Guinea Institute of Medical Research has come to our institute to undertake a Masters degree and will be investigating maternal and neonatal immune responses to *Streptococcus pneumoniae* and how these responses relate to early URT carriage in children in this study.

Enrolment of all 319 study participants was completed in September 2007. By December 2007 all children had completed follow-up to age 3 months and PCV vaccination. Data are currently being analysed to determine reactogenicity to the different schedules. W Pomat reported at an Indigenous Immunisation Research Workshop in August 2007 that preliminary data indicated that PCV was immunogenic when given at ages 1, 2 and 3 months.

In an extension of this project, D Lehmann is co-supervising a post-doctoral research fellow (IA Laing), who is investigating the contribution of human genetic susceptibility to nasal bacterial carriage, development of immune/vaccine responses and the incidence of pneumonia in this population. Dr Laing has an Australian Research Council Ann Woolcock Research Fellowship and genetics studies are supported through a grant from the University of Western Australia Research Grants Scheme 2006.

Genotyping of several immune gene polymorphisms on the first 66 DNA samples extracted from infants participating in the NPCV study has been completed. These results have proved very promising. They confirm that PNG children have significantly different frequencies of immune gene alleles compared to either a Caucasian population from Australia or one used in the HapMap project. Some of the genetic variants reportedly associated with respiratory infections in Caucasian children are more common in infants from PNG.

This study is funded by the NHMRC International Collaborative Research Grant Number 303123 and the Wellcome Trust, UK

Pathways to hospitalisation with infection

Deborah Lehmann, Hannah Moore, Peter Jacoby, Nick de Klerk in collaboration with David Burgner, Peter Richmond (School of Paediatrics and Child Health, University of Western Australia)

Following data analysis in 2005 and 2006 utilising the population-based WA Data Linkage System to investigate the principal reasons young WA children born between 1990 and 2000 are admitted to hospital, two key peer-reviewed articles were published in 2007. The first publication reported infection as the main cause of hospital admission in children aged less than 2 years, with admission rates for infection 4.6 times higher in Aboriginal children than in non-Aboriginal children. The second described the trends of acute lower respiratory infections and reported increasing hospital admission rates for bronchiolitis in infants aged less than 12 months between 1992 and 2000 and a diagnostic shift from asthma to bronchiolitis for children in their second year of life. Our findings were presented at several national and local conferences during the year including the Communicable Diseases Control Conference: "From outbreaks to pandemics in the region – building our capacity to respond" that was held in Canberra.

Funded by NHMRC, as part of NHMRC Program Grant number 353514, Theme 4: Infection

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, Kelly Watson, Christine Jeffries- Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane, Ruth Monck, Fiona Stanley in collaboration with Bega Garberringu Health Services Aboriginal Corporation, Ngnyntju Tjitji Pirmi Inc, Harvey Coates (Senior ENT Surgeon, Princess Margaret Hospital), Thomas V Riley (Department of Microbiology, University of Western Australia), Sharon Weeks (Audiologist, Professional Hearing Services), Allan W Cripps (Griffith University, Queensland), Jennelle Kyd (Central Queensland University, Rockhampton), Jacinta Bowman, Amanda Taylor, David Smith (Division of Microbiology and Infectious Diseases, PathWest Laboratory Medicine WA), Denise Murphy (Public Health Bacteriology Laboratory, Brisbane), Amanda Leach (Menzies School of Health Research, Darwin), Nevada Pingault (University of Western Australia)

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 was completed in April 2005.

The burden of OM remains very high in the Kalgoorlie-Boulder area with a peak prevalence of 72% in Aboriginal children aged 5-9 months and 40% in non-Aboriginal

children aged 10-14 months. Furthermore, 29% of Aboriginal children and 5% of non-Aboriginal children have 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.

A series of papers have been published in 2007. A paper detailing the rationale, methods, population characteristics and ethical considerations of the project has been accepted for publication. We have reported that for optimal isolation of *S. pneumoniae* and *H. influenzae*, transit time from collection in the field in Kalgoorlie to a -70°C freezer in Perth should be less than 72 hours and that *H. influenzae* grew better from nasopharyngeal aspirates than from nasal swabs. We also confirmed that pulsed field gel electrophoresis is the most appropriate molecular tool for the epidemiological study of *Moraxella catarrhalis*.

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. Using mathematical models we differentiated between host-level and pathogen-level interactions between different bacterial and viral pathogens which are relevant to determining the types of interventions required to reduce carriage and disease.

We found that exposure to environmental tobacco smoke is associated with increased risk of OM. A publication on these results will appear shortly in the Medical Journal of Australia.

Funded by Healthway; NHMRC Project grant number 212044 and as part of NHMRC Program Grant number 353514, Theme 4: Infection

Social, Economic and Psychological and Cultural Determinants of Health

The Western Australian Pregnancy (Raine) Cohort Study

The Raine Study Executive: Prof Ian Puddey (Chair), Prof Fiona Stanley, Prof Lawrie Beilin, Prof Lou Landau, Prof John Newnham, Prof George Yeoh.

The Raine Study is an ongoing longitudinal cohort study aiming to determine how events during pregnancy and around birth subsequently influence health and developmental outcomes. The study is following 2,860 Western Australian children born between 1989 and 1991 at King Edward Memorial Hospital in Perth. The one, two, three, five, eight, ten and thirteen year follow-ups of the cohort are completed. The Raine Study is currently conducting the sixteen year assessment. The cohort teenagers and their parents are sent a comprehensive questionnaire for completion. At the Institute the teenagers participate in a physical assessment as well as further on-line questionnaires and cognitive tests. The teenagers and the parents also provide blood and DNA samples. The main research areas for the sixteen year follow up include:

- Developmental health, physical, psychological and psychosocial characteristics
- Development of adolescent spinal pain,
- Physical activity, physical fitness, motor competence
- Cardiovascular health and blood pressure
- Polycystic ovarian syndrome and menstrual disorders

- Growth and nutrition
- Cognitive neuroscience, adolescent brain development
- Hypothalamic-pituitary-adrenal (HPA) axis functioning
- Non-alcoholic fatty liver disease
- To determine the prevalence of abnormal iron indices and hereditary hemochromatosis.
- To determine the prevalence of coeliac disease.
- Dietary patterns, mood and mental health
- Childhood precursors of adult cardiovascular disease and diabetes
- Asthma and atopy
- Gene-environment interaction

The Raine Study teenagers are now aged between sixteen and eighteen years of age and are involved in tertiary entrance examinations, apprenticeships, entering the workforce and beginning their adult lives. Their complex schedules, together with busy parents have made it increasingly challenging to recruit the participant families to the follow up. However they remain wonderfully committed to the Raine study and we are privileged to work with them. We have regular liaison with the Raine Study Youth Reference Group, who provide a valuable and insightful contribution to the management and running of the study.

The Raine Study 16yr follow-up is funded by the NHMRC (Stanley et al) Program Grant;.

The association between nutrition in infancy, childhood and adolescence and adolescent mood, mental health, cognition, stress responsiveness and immune function

Dr Wendy Oddy

Dr Oddy was recognised for her previous postdoctoral work when her NHMRC funded project 'The nutritional epidemiology of childhood asthma' was named as one of 'Ten of the Best' for NHMRC projects completed in 2004. In January 2008, Dr Oddy was named World Scientists Forum International Award "Eminent Scientist of the Year 2008" in the field of 'Paediatrics and Child Health Research' from Australia

Ms Therese O'Sullivan (a dietitian and exercise physiologist) joined the nutrition team in July 2007. Therese came from the Queensland Institute of Technology when she was in the final months of preparation of her PhD on glycaemic load and insulin resistance. Therese has since submitted her PhD and is working on the 3-day food diaries collected from the Raine cohort during the 14 year follow-up to ask similar research questions. Using the food diaries Therese will also be working on the omega-3 fatty acid hypotheses related to adolescent mental health.

An NHMRC Career Development Award that continued in 2007 allowed Dr Wendy Oddy to further investigations into nutritional associations with childhood development and morbidity

Childhood Precursors of Adult Cardiovascular Disease, Obesity and Diabetes - 16 year follow up of a Longitudinal Study

Prof Lawrence Beilin, Prof Lyle Palmer, Dr Wendy Oddy, Dr Trevor Mori, A/Prof Garth Kendall, Dr Beth Hands

This project aims to study the childhood and antenatal precursors for the risk of adult obesity, diabetes, heart disease and stroke. This study will provide comprehensive information on children from womb to adolescence and help pinpoint ways in which growth in the womb, and subsequent childhood behaviour interacts with influences of family, social factors, environment and mental health to affect long term risk of obesity, premature diabetes or heart disease. The study will also provide a basis for future examination of the links between genes, environment and health.

Funded by NHMRC: Project Grant

Dietary factors and trajectories of mental health from infancy to adolescence

Dr Gina, Ambrosini, Dr Wendy Oddy, Monique Robinson, Therese. O'Sullivan.

In 2007 Dr Gina Ambrosini joined the Nutrition team to work on the creation of dietary patterns from the Raine Study nutrition data. These patterns were derived from 212 usually eaten foods representative of the adolescent diet. A paper outlining this work has been submitted to the Journal of the American Dietetic Association titled 'Adolescent dietary patterns and their lifestyle and socio demographic correlates' for publication.

Funded by Australian Rotary Health Research Fund

Early child development and breastfeeding

Dr Wendy Oddy, A/Prof Garth Kendall, Dr Jianghong Li, Prof Nick de Klerk

In 2007 a draft of the manuscript 'The long-term effects of breastfeeding on adolescent mental health: a pregnancy cohort study followed for 14 years' was prepared for submission to a high ranking journal. Results of these analyses were presented at the joint Scientific Meeting of the Australasian Epidemiological Association and the International Epidemiological Association Western Pacific Region in September 2007 in Hobart, Tasmania.

In addition, Dr Oddy was invited to give a plenary session at the Developmental Origins of Health and Disease International meeting in Perth in November 2007 on research related to infant nutrition. This project formed part of the Nutrition theme of the Program grant investigating the long-term effects of early nutrition on later child health and development

Early life stress, adolescent brain development and risk for adverse cognitive and psychosocial outcomes

Dr Anke van Eekelen, A/Prof Jonathan Foster, Dr Eugen Mattes, Prof. E.R. de Kloet, Prof. I.W. McKeague

This project aims to study pre and postnatal childhood factors and examine their association with HPA-functioning, cognition, and mental health during adolescence in the WA Pregnancy Cohort Study (Raine Study). Childhood exposures include not only trajectories of stressful life events, family functioning and mental health status during childhood, but also effects of intrauterine and postnatal growth patterns and a comprehensive range of psychosocial, familial and environmental factors. It is our objective to characterise functional polymorphisms

for genes related to stress regulation and examine their interactions with early life exposures and their neurobiological consequences. We will also test 16 year old Raine subjects for cognitive ability and in some we will image their brain activity while performing these tests. We hypothesise that increased and sustained trajectories of early life stress, family dysfunction or poor mental health during childhood will increase the risk of Raine Study adolescents experiencing: 1) increased sensitivity with higher baseline cortisol levels during adolescence, 2) increased adolescent stress sensitivity, if they are carriers of specific haplotypes of the glucocorticoid and mineralocorticoid receptor genes, 3) depression during adolescence, if they are homozygous or heterozygous for the short allele of the serotonin transporter (5-HTT) gene, 4) poorer cognitive performance and increased atypical non-prefrontal cortex (PFC) brain activity during cognitive testing as measured by fMRI; and 5) more mental health problems during adolescence.

Funded by NHMRC: Project Grant

Physical, lifestyle and psychosocial determinants of spinal pain development in adolescents - 16 year follow up of a Longitudinal Study (2005-2008)

A/Prof Leon Struiker, Dr Peter O'Sullivan, A/Prof Garth Kendall

The purpose of this project is to develop a clearer understanding of the complex development of spinal pain disorders in childhood and adolescence in order to inform the creation of new, effective and cost-efficient preventive and therapeutic interventions.

Funded by NHMRC: Project Grant

Gene Environment interactions underlying DOHAD. Analysis of stress-induced levels of stress hormone in human blood and saliva of 18 year-old members of the Raine study

Prof Steven Lye, Prof Lawrie Beilin, Dr Steven Zubrick, Prof Fiona Stanley, Prof John Newnham, Prof Lawrie Palmer, Dr Anke van Eekelen, Dr Craig Pennell,

The overall objective of this project is to define gene-environment interactions that underlie the developmental origins of health and disease. Increasing evidence suggests that premature activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis is a central component linking adverse ante- and post-natal environmental exposures to the metabolic syndrome, obesity, neurologic disorders and mental illness. Within the Raine-cohort we aim to profile stress-induced HPA activity at 18 years of age using the Trier Social Stress Test. We aim to test 1000 Raine participants and relate their stress-induced HPA function to resting HPA activity as assessed at 16 years of age in these participants.

We also aim to identify polymorphisms within genes that regulate the function of the HPA axis in the children and their parents within the Raine cohort and to analyse the relationship between genotype, environmental modifiers and marker of adverse health outcomes.

Funded by CIHR Project Grant

The fetal and early childhood origins of polycystic ovary syndrome. A prospective cohort study

Prof Martha Hickey, A/Prof Roger Hart, Dr Deb Sloboda, Dr Dorota Doherty, Dr Michael Davies, Prof Stephen Franks

The polycystic ovary syndrome (PCOS) affects up to 10% of women of reproductive age. The underlying causes of PCOS are unknown but are thought to arise during intrauterine (fetal) life and to be modified by aspects of childhood health, particularly overweight and obesity. Using the Raine Cohort, the researchers will define for the first time the intrauterine and early childhood correlates of PCOS. The results from these studies will improve the understanding of PCOS and eventually improve reproductive and metabolic health for a substantial proportion of women internationally.

We have now completed our recruitment and 252 girls have been enrolled in the Raine Study. Data on ovarian morphology, timed sex steroid levels and clinical and biochemical hyperandrogenism have been collected and are currently being analysed. Ovarian morphology has been classified into "PCOS" or "normal" based on standardized criteria.

This year we will complete the following data collection:

- Ultrasensitive analysis of adolescent androgens
- Urine testing for pregnanediol to exclude ovulation in those with irregular menstrual cycles
- Completion of prospective menstrual diaries

When we have these data we will be able to assign our cohort to the PCOS or non-PCOS categories and can then address our study hypotheses

Funded by NHMRC Project Grant

Antenatal and perinatal determinants of mental health in childhood and adolescence in the Western Australian Pregnancy Cohort (Raine) Study

Monique Robinson

PhD Project. This project examines the effects of various antenatal risk factors on child and adolescent mental health outcomes using data from the Western Australian Pregnancy Cohort (Raine) Study. The project commenced in early 2007 and is now in its second year with completion estimated by late 2009.

The first paper to come out of this research looks at a wide variety of pre-, peri- and postnatal risk factors for behavioural problems in the pre-school years, and is currently under review. The strongest risk factors in this study were antenatal stress, maternal smoking in pregnancy, low family income, and more "baby blues" symptoms immediately after birth. This work was presented as a poster at the Developmental Origins of Health and Disease (DOHaD) International Congress in Nov 2007. I received funding from ARACY & ARC/ NHMRC to attend the DOHaD congress.

The second paper examines the effect of maternal gestational hypertension and preeclampsia on child and adolescent behaviour, and is due for submission early in 2008. We found that maternal gestational hypertension increases the risk of behavioural problems in offspring from ages eight to 13. This research was presented as an oral presentation at the DOHaD congress, and has been accepted for the International Society for the Study of Behavioural Development congress in July 2008. I have received an Australasian Human Development Association (AHDA) scholarship to attend the congress.

The next phase of the project involves an analysis of

maternal cigarette smoking, alcohol consumption and caffeine intake in pregnancy in relation to later mental health outcomes, and a close examination as to the role of antenatal stress in child and adolescent behavioural development.

Funded by University Postgraduate Award (UPA), Stan and Jean Perron Award, ARACY & ARC/NHMRC Early Career Researcher Scholarship, AHDA Scholarship for ISSBD 2008

Early Development Instrument – International Consortium

Sally Brinkman, Clyde Hertzman, Magdalena Janus, Fraser Mustard, Mary Young and Sharon Goldfeld.

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 Oxford 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 and Madagascar, with countries such as China, Bangladesh and Mongolia showing interest.

Funded by WorldBank

WA Reproductive Health Study (Virtual Infant Parenting Program)

Sven Silburn, Sally Brinkman, David Lawrence, Jim Codde, Bret Hart and Judy Straton

The Virtual Infant Parenting Program (VIP) is a six-day health promotion program where teenage participants learn about pre-conceptual health, pregnancy, childbirth, and the practical realities of caring for a young infant. The program covered health issues affecting infant and maternal health, such as smoking, nutrition, alcohol and other drugs, physical activity and support systems. A key component of the program was to care for an infant simulator over a weekend period. The program's effectiveness is being evaluated via a clustered randomised control trial where participants are now being tracked through the Western Australian Data Linkage Service for child and maternal health outcomes. In addition, for those participants that have a live birth during their teenage years, home interviews are being conducted to determine the level of impact the program had on pre-conceptual health, pregnancy and child birth.

Funded by Department of Education and Training, Department of Health.

Centre for Developmental Health

Centre for Developmental Health

Silburn S, Zubrick S, D Lawrence, K Taylor

The Centre for Developmental Health is a joint venture between Curtin and ICHR for the establishment of a centre of expertise in developmental health research. The Centre promotes the integration of knowledge of human growth and development across traditional discipline boundaries and the application of this knowledge for the

advancement of children's developmental outcomes. Our goal is to develop a knowledge base to assist society to move towards greater equality of health and opportunity for children and young people—i.e. improve health and the develop their capacities and skills, and to promote a competent population at all socio-economic levels.

Restor(y)ing Aboriginal Parenting (TOO SOLID)

Zubrick S, Silburn S, Donovan R, D'Antoine H, Kickett-Tucker C, Milroy H, Milroy J, Lawrence D, Wilkes E, Cox A, Pearson G (resigned), Bessarab D, Woods L, Penny F,

The Restor(y)ing Aboriginal Parenting Project involves the development and evaluation of a culturally relevant program for Aboriginal parents of young children. It aims to address the intergenerational effects of past policies of forced separation of children on the cultural and social transmission of parenting knowledge and skills. It seeks to restore identification with culture, promote parental confidence, knowledge and child rearing skills and enhance resilience in Aboriginal children.

This five year NHMRC Research project commenced in 2006 supported by a budget of \$2,104,620, with contributions from NHMRC \$1,612,793, and Curtin University \$491,827)

Twins and Singletons with Specific Language Impairment (LOOKING at Language)

Rice, M. (Institute for Lifespan Studies, University of Kansas), Taylor C., Zubrick, S. (Centre for Developmental Health, Curtin University of Technology and Telethon Institute of Child Health Research), Smith, S. (University of Nebraska Medical Center)

The LOOKING at Language project aims to understand

why some children have difficulty developing language and later in learning to read. LOOKING at Language is a joint initiative between the Telethon Institute for Child Health Research, Curtin University of Technology and the USA's University of Kansas and University of Nebraska Medical Center. LOOKING at Language began as a 5-year study (2002-2007) of language development from 2-6 years of age, funded by the USA National Institutes of Health. In July 2007, the study was funded by the USA National Institutes of Health for a further 5 years (2007 – 2012), allowing us to study children from 2-9 years. The additional funding enables us to continue our study into the vital early years of school and to begin molecular genetic studies of language, speech and reading disorders. The project conducts in-depth and comprehensive assessments of language development at 2, 4, 6 and 9 years and literacy skills at 6 and 9 years. These ages are benchmarked to the critical early learning years between kindergarten and Year 3.

Results so far for single-born children, point toward characteristics of the child as important predictors of language delay at 2 years and away from characteristics of the child's family environment, such as the mother's level of education, income or parenting style. One family factor that was important was whether or not anyone else in the family had a history of language delay. Our results show that most children (80%) with early language delay catch up by school age. However, 20% of the children we studied did not catch up. Our research will help explain why some children struggle with language development and later with reading.

This project will help explain why some children have difficulty developing language and later in learning to read. Most children with normal hearing, normal intelligence and no other developmental problems

develop language with remarkable ease, however 7% of children do not and the causes are currently unknown. Knowledge about genetic and environmental pathways to language disorders and reading disorders will translate to improved early identification of children at risk for language and reading disorders and improved service provision for children in the health and education sectors.

Funded by National Institutes of Health (NIH) via a subcontract with Curtin University of Technology and the University of Kansas Centre for Research

Suicide Prevention

WA Ministerial Council for Suicide Prevention

Silburn S (Chair), Phillips S (Executive Officer), Robertson D, Northey K, Miller K, Mudgway N, Hillman S, Gibbs C, Bromley L, Cangemi T, Jordan S.

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 Council is administratively based at the Institute and reports to the Minister for Health. It includes senior representation of all government departments concerned with human services, non-government agencies, carers, consumers and other community stakeholders. The Council is responsible for advancing scientific and community understanding of suicide and its prevention and seeks to co-ordinate the efforts of government and community sector services in reducing the morbidity and mortality associated with suicide and self-harm.

A highlight of 2007 was a State wide consultation process, in collaboration with the Mental Health

Division, the Office for Children and Youth, Regional Mental Health Services and Aboriginal Medical Services, to inform the development of a five year State Suicide Prevention Strategy. Eighteen consultation events were hosted across WA, including several rural and remote locations. The draft WA State Suicide Prevention Strategy 2008-2013 was presented to the Minister for Health in November 2007.

An important highlight in 2007 was the Council's success in winning a \$1.13 million National Suicide Prevention Strategy competitive research grant (2007-2009) to develop and evaluate an innovative proactive bereavement support service. The ARBOR (Active Response Bereavement OutReach) Service for people bereaved by suicide was developed in 2007 and launched in October of that year. 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.

NSPS Funding of \$68,000 was granted to reprint the valuable suicide bereavement resource entitled "Information and Support Pack for those bereaved by suicide or other sudden death". The resource is currently available in WA, NT, SA, VIC, QLD and ACT and is also available online at www.mcsp.org.au/bereavement_pack

Integrated proactive suicide bereavement postvention project

Prof Sven Silburn, Mr Brian English, Mr Shawn Phillips

Early intervention is important to assist in normalising the grief process, to facilitate the identification of those more at-risk, and to reduce the risk of suicide and suicidal behaviours amongst those bereaved by Suicide.

Funded by Commonwealth Department of Health and Ageing

The Applied Research Projects in Child Health

ADHD Raine project

Mr Kim Clark, Tanyana Jackiewicz, Mr Grant Smith, Rachel Skoss

The current study aims to meet two objectives: 1) to identify early predictors and possible causative factors in the development of ADHD, and 2) to examine the long-term effects (both positive and negative) of the use of stimulant medication in the treatment of ADHD.

To explore the early predictive/causative factors in the development of ADHD, a number of factors measured during the prenatal period and early childhood have been examined with reference to an eventual diagnosis of ADHD. Currently only bivariate associations between these factors and ADHD have been completed (significant prenatal measures are: mothers age at time of child's birth, family structure, family income, mother's physical activity, and whether the mother smoked during pregnancy). The next stage for this objective is to construct a multivariate model to examine the independent effects of each of the factors on an eventual diagnosis of ADHD). To examine the long-term effects of stimulant medication in the treatment of ADHD a

number of analytical methods are being employed. The first method is to construct a number of multivariate models, using only children diagnosed with ADHD, that predict a number of outcomes (social, emotional, academic, physical) and include the use of stimulant medication as a predictor variable (whilst controlling for symptom severity). These models have been run and the results tend toward children on stimulants having poorer outcomes than non-medicated ADHD-diagnosed children: however, there is a very strong doubt as to whether symptom severity can be sufficiently accounted for, which would mean these models are not valid (other avenues of controlling for symptom severity are being explored). The second method uses norm-referenced measures to examine whether there was any long-term improvement in social/emotional/academic functioning after the commencement of stimulant medication. The third method follows 'problem' children (identified as those with behavioural/attentional at the age of 5) to see who are diagnosed with ADHD, who went on medication and comparing the outcomes of these children at age 13. Preliminary results for these final two methods are available, which appear to indicate no large differences associated with stimulant medication. It should be emphasised that these results are still preliminary and are yet to be finalised. Analysis and interpretation is aimed to be completed by mid-February 2008, making the results available to present at the next meeting of the Stimulant Sub-Committee of the Parliamentary Inquiry into ADHD in WA Implementation Committee. West Australian Department of Health

An exploration of the experience of families along the pathway to a diagnosis of ADHD in children

Stephanie Jackiewicz, Tanyana Jackiewicz

There has been controversy about the rates of children being diagnosed with ADHD and the subsequent prescription of stimulant medications. In the US significant regional differences have been identified in relation to the prescription of stimulant medication for the treatment of ADHD (Sax, 2003). In Australia, Western Australia (WA) has been identified as having a higher rate of stimulant prescription than any other state. In WA only highly trained specialists (Paediatrician or Child, Adolescent Psychiatrist or Paediatric Neurologist) are able to initiate treatment with stimulant medicines in children with a diagnosis of ADHD. There are strict guidelines that these specialist apply when making this diagnosis. Despite this, ADHD is an emotive topic for many families and one that is fuelled by media interest. To date there has been a significant amount of research into the general area of ADHD; however, gaps remain. One area where gaps remain in the ADHD research is in the pathways to diagnosis. Research conducted in the US discovered that it is teachers or school personnel who are most likely to be the one to first suggest the diagnosis of ADHD (Sax, 2003). Among the elements which challenge health care providers is that parents and teachers tend to make different judgements about ADHD symptoms in the same children (Nijs et al, 2004). Jackson and Ring (2004) also pointed to differences in teacher ADHD ratings of the same behaviours among boys and girls. Foy and Early (2005) have also pointed to barriers to access in ADHD treatment pathways for the economically disadvantaged and some ethnic groups. Further along the ADHD treatment pathway, Sayal et al (2002) have highlighted the need for clearer treatment referral protocols for

general practice in the UK. These issues may also apply in the local environment. In the local setting Taylor et al, 2006 conducted a study in WA to identify the decision making process of parents to medicate their child or not. They identified a three stage approach that parents move through in this process.

This project is currently in the recruitment stage. Contact with pediatricians has occurred and the TICHHR is awaiting contact with families. Once families have been recruited a research officer will interview the families.

Alternative recruitment strategies are currently being considered.

Funded by Health Department of WA

CATI themed reports

Clark, K, Jackiewicz T.

The TICHHR has prepared policy relevant evidence reports on specific issues related to children living in Western Australia. The Themed Reports have been developed according to the following: 1. That the preparation of the reports be considered a collaboration between the ICHR and the DoH. This means that the proposed report will be jointly badged as an ICHR-DoH product; 2. That the reports be structured in such a way that it presents data in a form that is relevant to the various DoH administrative Areas and Regions; and 3. That the report be oriented to providing data that has decision making value.

The Institute has analysed Western Australia Health and Wellbeing Surveillance Data as well as ABS and other datasets to produce six themed reports:

Themed reports include:

- A profile of Western Australian children
- A Healthy Start to Life
- Health Conditions
- Health Care needs
- Health Care Services
- Health Behaviours.
- West Australian Department of Health

Healthy Babies for Mothers with Serious Mental Illness: A case management framework for clinicians

Tanyana Jackiewicz, Dr Yvonne Hauck

In a recent WA study of pregnancy and birth complications among mothers with a serious mental illness (SMI) conducted by the Centre for Clinical Research into Neuropsychiatry (CCRN) and TICHHR it was found that this group do not routinely access antenatal services. As these mothers are at high risk for pregnancy and birth complications that increase neurodevelopmental risks for their babies, their failure to access antenatal care is significant health issue. Both the WA study and several similar studies in other countries have established that the absence of monitoring factors such as folate supplementation and lifestyle and health decisions, such as diet, smoking, alcohol and other drug use contributes substantially to the generally poorer pregnancy outcomes in this group. In terms of possible strategies to address the failure to access antenatal care among these at risk women, is noteworthy that during the course of their pregnancy, many remain in contact with mental health

services. It is also relevant to note that community mental health nurses (CMHN) have demonstrated a capacity to deliver off the shelf health care packages to at risk groups. The purpose of this project is to develop a clinical framework directed to improving reproductive health outcomes for women with SMI for use by community mental health clinicians. The framework emphasises factors that are amenable to intervention, including antenatal care attendance, tobacco use, nutrition, and early access to support services. The framework will be launched in mid 2008.

Funded by North Metropolitan Area Health Service

Evaluation of a policy reform consultation process in Maternity Services

Tanyana Jackiewicz, Dr Colleen Fisher

The Maternity and Neonatal Clinical Network is undertaking a consultation process for the Future Direction in Maternity Care Plan (FDMC) in Western Australia. The goals for the evaluation are as follows: 1. To describe the consultation process as it is being undertaken; 2. To profile stakeholder views of the consultation in terms of quality, inclusiveness, acceptability, and impact (addressing those set out in the consultation plan as well as other issues); 3. To assess the overall merits (as well as outcomes) of the consultation with reference to the available scientific evidence (best practice); 4. To make specific recommendations about methods and delivery of the consultation as per best practice; 5. To develop a set of best practice guidelines for future consultations within the Western Australian Health System. The evaluation has been completed and the best practice guidelines will be available in early 2008.

Injury and Trauma Profile Project

Clark, K, Jackiewicz T.

The TICHR is working with the Injury and Trauma Clinical Network to undertake data analysis project around investigating trends in head injury and hospitalisable burns. The aim of this study is to describe the prior medical history, family history and characteristics of a cohort of Western Australian children who have had a hospital admission for a burn or head injury and compare this data to that obtained for a matched control cohort of children admitted to hospital as a consequence of other causes. The outcomes of the proposed study will be ascertainment of indicators that could be used to identify children who have an elevated risk for serious burns or head injuries. These indicators could subsequently be used to assist with the design of community based preventive interventions. This project is underway.

Promoting Optimal Infant Nutrition: The Perth Breastfeeding Scoping Project

Mr Grant Smith, Tanyana Jackiewicz, Sally Brinkman, Dr Wendy Oddy, Dr Yvonne Hauck, Assoc Prof Nadine Henley, Ms Pernilla Ellies, Brett Hart, Colin Binns

The overall aim of this project is to gather information that will allow effective planning of a contextual, multi-level, and collaborative health promotion strategy for breastfeeding in the North Metropolitan Area of Perth (NMAHS), Western Australia. Focus groups with first time mothers of 6 month old babies regarding their breastfeeding practices; beliefs, knowledge and attitudes that impact upon these, and external barriers and facilitators that informed and influenced their choices have been conducted. Results will be analyzed in early 2008, and interview with key informants, regarding the

barriers and facilitators to breastfeeding within the broader social contexts in which mothers live and work will be undertaken. Final report to be prepared by April 2008.

Funded by Western Australian Health Promotion Foundation (Healthway)

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Somer Dawson, B Econs B Hlth Sci (Hons)

Jan De Groot, BAppSci (MedTech). MPH

Professor Nick De Klerk, BSc, MSc, PhD

Katherine Di Candilo, BSc (Hons) APD

Alex D'Vauz, BSc Hons

Glenys Dixon, BA, BPsych, MPsych(Clinical)

Dr Jenny Downs, Ph D

Smilja Dragovic, BPsych

Paula Dyke, BAppS, (Physio) MPH

Tracey-Lee Edwards, Dip (PR)

Julie Fedele, BA, DipEd, BA Psych (Hons)

Marty Firth, BSc (Hons)

Kathryn France, BSc (Hons)

Jane Freemantle, RN, MPH, PhD

Sue Ferguson-Hill, RN, CM, C&FHN, MMid
(Distinction), MPH

Dr Bess Fowler, BAppSc (Occupational Therapy), MSc
(Health Sciences), PhD

Dr Lisa Gibson, BA (Hons) MPsych (Appl Develop)
PhD

Lucy Giggs, BHealthSci/BCommerce

Dr Emma Glasson, Bpsych, BSc (Hons), PhD

Peta Gooda

Tegan Grace, BSc

Suzanne Green, REN, Phleb

Dr Erika Hagemann, BSc (Speech and Hearing Science)
Hons, PhD, CPSP

Stephanie Hall

Janice Hansen, MPH, BSc (Hons)

Catherine Harrison, RN

Anna Hepworth, BSc hons (Psych). BSc Hons
(Math&Stat)

Emily Hockley, BSc

Derry Houston, BA / MSocWk

Amber Howard, BSc (Psychology) Hons

Antonietta Grant, Psych

Stephanie Jackiewicz, B.Soc.Sci (CS) M.Soc.Sci

Tanyana Jackiewicz, BSc (Hons), MPH

Peter Jacoby, BA (Hons), MSc

Le Jian, MBBS, PhD

Dr Cheryl Kickett-Tucker, PhD

Dr Ingrid Laing, BSc, PhD

Crystal Laurvick, BA MPH

Dr David Lawrence, BSc, PhD, ATCL

Roseline Lee, BSc (Pathology and Microbiology)

Associate Professor Deborah Lehmann, MBBS MSc

Associate Clinical Professor Helen Leonard, MBChB,
MPH

Dr Jianghong Li, BA, MSci, PhD, (Senior Research
Fellow) up to 31 September 2007

Jacqueline Mansour, BSc MPH

Dr Eugen Mattes, MBBS, MPH, PhD, FRACGP

Daniel McAullay, BSc (Nursing), MAE

Stephanie McBeath, RN, BA (Psych) (Hons)

Megan McClurg, BSc, MSc (SpPath)

Meg McHugh, BSc, MSc

Anne McKenzie, Consumer Consultant

Kate Miller, BSC, MHP (Health Promotion)

Dr Elizabeth Milne, BAppSc (Physio), MPH, PhD

Heather Monteiro, BA SocSci, MPH

Hannah Moore, BSc (Hons I) GradDipClinEpid

Jenny Mountain, BA, MBA

Nikki George (Mudgway)
 Virginia Muniandy, BEd (Early Childhood)
 Dr Natasha Nassar, BEd, MPH, PhD
 Fiona Nichols, PhD
 Kristine Northey, BAppSc (Psych), RMHN,
 PGradDipHlthSc, MSc (Pub Health)
 Colleen O'Leary, RN, BSc, MPH
 Dr Wendy Oddy, BAppSci (Nutrition) MPH, PhD, NHMRC
 Population Health Research Fellow, University of Western
 Australia Adjunct Research Fellow, Telethon Institute for
 Child Health Research Honorary Research Fellow
 Kristy Officer, BSc BVMS
 Rani Param, BSc (Health Promotion)
 Jan Payne, SRN(UKCC), P Grad Dip (Hlth Admin), MSc
 (Pub Hlth)
 Carol Phillippe, RN
 Shawn Phillips, BTh, MSWAP
 Janine Pickett, (dec'd)
 Alani Pike, TA EDWA
 Michelle Quail, RA
 Deborah Robertson, BA, DipEd, MPhil
 Myra Robinson, B.Hlth.Sc (Hons)
 Monique Robinson, BA (Hons) Psych, Grad Dip Comm,
 M.Psych (Clinical) candidate
 Kylie Rooney, RN
 Fiona Salter, BSc (Hons), Nutrition & Dietetics
 Marg Sayers, RGN Grad Dip (Health Sciences), Cert

Addiction Studies
 Elke Scheepers, BA, AdvCert Tvl Cons
 Dr Clair Scrine-Bradfield, BA (Hons), PhD
 Dr Rachel Skoss, BSc, PhD.
 Ellen Seymour, MSocSc
 Carrington Shepherd, BA (Econs)
 Professor Sven Silburn, BSc(Hon) MSc(ClinPsych) MAPS
 Nick Sloan, BSc Hons
 Carolyn Smargiassi, Data Entry Clerk
 Amy Smithies,
 Grant Smith, BPsych, M Psych
 Michael Smith, BSc
 Michaela Stone, BA(Psych), MSc(SpPath)
 Associate Professor Kate Taylor, BAppSc, PGradDipHlthSc,
 PhD, FSPA
 Mary Tennant, RN RM BAppSc MPH
 Theresa Venz, BA (Hons)
 Dr Roz Walker, PhD, BA (Hons) Politics and Philosophy
 Alicia Watkins, BPsych, PGradDip. (Psych).
 Linda Watson
 Felicity Watt, B.Psych, MSc
 Dr Katie Watts (Suriano), BSc (Hons) PhD
 Associate Professor Ted Wilkes, BA (Social Science)
 Anwen Williams, BEd (PhysEd)
 Melanie Williams

Jude Willis, BAppSc GradCertPubHlth GradDipHlthSc
 Margaret Wood, BA(Hons), MA, MBCS, CITP
 Diane Wood, BAppSc (Phys Ed) Dip Ed, Grad Dip HN
 Professor Steve Zubrick, MSc, MA, PhD
Postgraduate Students
 Karina Allen, B.A. (Hons) PhD Candidate
 Lyn Colvin, BCom, MPH, PhD candidate
 Adele Cox, DipAppSc, MMedSci Candidate UWA
 A Ferrante, BA, Dip Ed, PhD candidate
 Noula Gibson, BAppSc(Phys)(Honours);
 PostGradDip(Phys)(Dev Paeds); MSc (Phys Dev Paeds)
 Michelle Hansen, B.Sc, MPH, PhD candidate
 Dr A Haynes, MBBS, MPH candidate
 Amanda Jefferson, MPH candidate
 Jocelyn Jones, BPsych, Msc (Clin Psych), PhD candidate
 Amanda Langridge, BSc (Hons), PhD candidate
 Sarah Love, BApp Sc(phys), PostGradDip Phys(Dev Paeds)
 Eva Malacova, BSc (Hons), MSc (Applied Statistics), PhD
 candidate
 Hannah Moore, BSc (HonsI) GradDipClinEpid, PhD
 Candidate
 Kristine Northey, BAppSc (Psych), RMHN,
 PGradDipHlthSc, MSc (Pub Health), PhD Candidate
 Melissa O'Donnell, BPsych (Hons), MPsych, DipEd, PhD
 candidate
 Colleen O'Leary, RN, BSc, MPH, PhD candidate
 Glenn Pearson, BA (Ed), Masters candidate

N Pingault, BSc(MedSci)(Hons I) MASM MAIMS PhD Candidate

William Pomat, BSc(Hons) MSc PhD Candidate

Monique Robinson, BA (Hons) Psych, Grad Dip Comm, M.Psych (Clinical) candidate

Honorary Research Fellows

Dr Rachel Skinner, MBBS PhD FRACP

Dr Jianghong Li (since 1st Oct. 2007), BA, MSci, PhD

Theses passed

Rose Barnes, B Health Sci, UWA 2007. Assessing the consistency between a general health questionnaire and a food frequency questionnaire regarding maternal folate intake in and around pregnancy

Anke Bergmann, MPH The development of clinical guidelines for the management of scoliosis in Rett syndrome

Sandra Louise, BSc (Hons) How representative of a national Rett syndrome population is the InterRett international cohort?

Heather Monteiro, MPH, UWA 2007. Consumer and Community Participation in Health Research

Janice Hansen, PhD, The Western Australian Register of multiple births: a twin-family study of asthma. (in conjunction with UWA Population Health)

Felicity Watt, Masters, Measures of adiposity for predicting mental health outcomes in children and adolescents. (in conjunction with UWA Psychology)

Awards

Clinical Professor Carol Bower, NHMRC Principal Research Fellowship 2005-2009

Heather D'Antoine, Harper Sisters' Fund Travel Award

Heather D'Antoine, Dr Louisa Alessandri Award for Excellence and Commitment in Research

Kathryn France, Healthway Health Promotion Research Training (PhD) Scholarship and Australian Postgraduate Award (relinquished).

Kathryn France, National Health and Medical Research Council Public Health Postgraduate Scholarship

Kathryn France, Edith Cowan University Excellence Award

Colleen Hayward, WA Telstra Business Woman of the Year (Finalist)

Jocelyn Jones, Indigenous Postgraduate Top-Up Scholarship

Dr Deborah Lehmann, Appointed Fellow of the Papua New Guinea Institute of Medical Research Port Moresby, PNG Sep 2007

Dr Deborah Lehmann, Lifetime member of the Medical Society of Papua New Guinea Port Moresby, PNG September 2007

Dr Jianghong Li, Curtin University Research Fellowship December 2006 (2007-2011)

Dr Natasha Nassar, NHMRC Postdoctoral (Public Health Australian) Fellowship 2006-2009

Dr Natasha Nassar, Qantas New Investigator Award 2007

Dr Natasha Nassar, Alessandra Lisi Memorial Prize for

Scientific Publication 2007

Kristine Northey, ARHRF/Rotary Club of Sydney CBD: Nathan's Bequest PhD Scholar for 2007

Colleen O'Leary, Alcohol Research and Education Foundation Travel Award

Dr Wendy Oddy, NHMRC Population Health Career Development Award 2005 to 2009 (\$425,250)

Dr Wendy Oddy, World Scientists Forum International Award " Eminent Scientist of the Year 2008" in the field of 'Pediatrics And Children Health Research' from Australia.

Glenn Pearson, Indigenous Postgraduate Top-Up Scholarship

Dr Katie Watts, National Heart Foundation Pediatric Postdoctoral Research Fellowship 2007-2008

External Committees

State

Jason Barrow, Link Person, Cooperative Research Centre for Aboriginal Health

Jason Barrow, Member, TICHR Reconciliation Working Committee

Associate Professor Eve Blair, Shaken Baby Syndrome Steering Committee

Associate Professor Eve Blair, Member: Scientific Advisory Sub-committee to the Princess Margaret Hospital for Children Ethics Committee

Clinical Professor Carol Bower, WA Perinatal and Infant Mortality Committee Member 1988-1992, 1993-

Clinical Professor Carol Bower, Scientific Sub-

Committee of the Human Research Ethics Committee, Curtin University of Technology 2000-

Clinical Professor Carol Bower, Western Australian Genetics Council, Department of Health WA, 2001-

Clinical Professor Carol Bower, Prenatal Diagnosis Committee, Department of Health WA, 2001-

Tracey-Lee Edwards, Member, Asthma Foundation NAPS - Indigenous Women's Project Reference Group

Tracey-Lee Edwards, Member, The Foundation for Young Australians Board

Tracey-Lee Edwards, Member, Central TAFE Governing Council

Associate Professor Jane Freemantle, Member Princess Margaret Hospital Mortality Review Committee

Associate Professor Jane Freemantle, Observer, Victorian Consultative Council on Obstetric and Paediatric Mortality and Morbidity, 2004-

Associate Professor Jane Freemantle, Ministerial Advisory Council on the Prevention of Death in Children and Young People

Associate Professor Jane Freemantle, Member Scientific Advisory Council SIDS and Kids, (WA)

Associate Professor Jane Freemantle, Member of the WA Board of the Australian Council on Smoking and Health

Associate Professor Jane Freemantle, Member WA Branch Executive of the Public Health Association of Australia

Associate Professor Jane Freemantle, Jalaris Aboriginal Corporation – Adviser to programs, evaluation and funding

Associate Professor Jane Freemantle, Convenor and Chair

of the Caitlyn Anne Foundation Working Group

Sue Ferguson-Hill, Member, AHCWA Aboriginal Health Promotion Advisory Group

Associate Professor Colleen Hayward, Member, WA State Training Board

Associate Professor Colleen Hayward, Member, National Heart Foundation - WA Board

Associate Professor Colleen Hayward, Deputy Chairperson, WA Constitutional Centre

Associate Professor Colleen Hayward, Member, Selection Panel for Community Services Industry Awards

Associate Professor Colleen Hayward, Deputy Chairperson, Aboriginal Advisory Committee to the Centre of Aboriginal Studies, Curtin University

Jocelyn Jones, Child Death Review Committee

Jocelyn Jones, Western Australia Aboriginal Health Information Ethics Committee

Dr Deborah Lehmann, Meningitis Centre Committee (1998-)

Dr Deborah Lehmann, Princess Margaret Hospital Ethics Committee (2005-)

Dr Deborah Lehmann, Perinatal and Infant Mortality Committee, Ministry for Health, WA (2005-)

Dr Deborah Lehmann, Western Australian Department of Health Communicable Disease Control Directorate Strategic Advisory Group 2007-

Anne McKenzie, Deputy Chair and Board Member, Health Consumers' Council WA Inc. 2003-ongoing

Anne McKenzie, Member, Health Consumers Council WA Inc. 1994- ongoing

Anne McKenzie, Consumer Representative, Primary Health Care Research Evaluation and Development Unit Advisory Committee. University of Western Australia, Notre Dame University and Combined Universities Centre for Rural Health. 2005-ongoing

Anne McKenzie, Consumer Representative Royal Perth Hospital Intensive Care Research. 2005-ongoing

Anne McKenzie, Consumer Representative Child & Youth Health Clinical Network. 2006-ongoing

Anne McKenzie, Lay Member, Silver Chain Ethics Committee, Perth. 2005-ongoing

Anne McKenzie, Consumer Representative Western Australian Audit of Surgical Mortality Management Committee, Royal college of Surgeons. 2006 ongoing

Glenn Pearson, Member, Consumer and Community Participation Council

Glenn Pearson, Health Council of Western Australia Inc

Dr Wendy Oddy, Infant and Early Child Nutrition Working Group, HDWA, 2007-2009

Dr Wendy Oddy, Chairperson, Baby Friendly Hospital Initiative Advisory Committee (WA), 2003-2007.

Dr Wendy Oddy, Baby Friendly Hospital Initiative Assessor, Qualified March 2004; assessed King Edward Memorial Hospital June 2007 in a team of 3 assessors, assessed Kalgoorlie December 2007.

Dr Wendy Oddy, Chairperson, Breastfeeding Public Health Promotion campaign, North Metropolitan Health Service, Western Australia, 2005-current.

Dr Clair Scrine, Member, Western Australian Immunisation Alliance

Professor Sven Silburn, Mental Health Network

Coordinating Committee

Professor Sven Silburn, WA Mental Health Safety Action Group

Dr Roz Walker, Member, Steering Committee for Indigenous Maternal and Child Health Service Research (NHMRC), School of Nursing and Midwifery, Curtin University of Technology

Dr Roz Walker, Invited Member, Executive Committee, Hedland Youth Stakeholder Action Group, Indigenous Coordinating Committee

Dr Roz Walker, Invited Member, Newman Local Drug Action Group

National

Dr Susan Byrne, Member of The Australian Child and Adolescent Obesity Research Network (ACAORN) (2004)

Dr Susan Byrne, Co-chair of the ACAORN Longitudinal Studies Special Interest group (2004)

Dr Susan Byrne, Member of the Australian Eating Disorders Research Interest Group (2004)

Associate Professor Eve Blair, National committee for Australasian Academy of Cerebral Palsy and Developmental Medicine.

Associate Professor Eve Blair, Scientific advisory committee for 3rd International CP Meeting. Sydney, Feb 2009

Clinical Professor Carol Bower, Australian Birth Defects Society Committee member 1986, 1999 -

Clinical Professor Carol Bower, Australian Paediatric Surveillance Unit Scientific Review Panel 1998-

Clinical Professor Carol Bower, Australian Paediatric Surveillance Unit Board 1998-, Chair (2003-)

Clinical Professor Carol Bower, National Child Health Information Advisory Committee (AIHW) 1998-

Clinical Professor Carol Bower, Intergovernmental Committee on Drugs Working Party on Fetal Alcohol Spectrum Disorder – member 2006-

Clinical Professor Carol Bower, Food Standards Australia New Zealand, Folate Fortification Scientific Advisory Group 2006-

Associate Professor Jane Freemantle, Fellow of the Public Health Association of Australia

Associate Professor Jane Freemantle, Member of Australian Mortality Data Group

Associate Professor Jane Freemantle, Member National Child Death Review Group

Associate Professor Jane Freemantle, Vice-President (policy) Public Health Association of Australia

Sue Ferguson-Hill, Clinical Associate of the New South Wales College of Nursing

Associate Professor Colleen Hayward, Life Member, Aboriginal Education Committee of the Australian Education Union

Associate Professor Colleen Hayward, Deputy Chairperson, Ministerial Advisory Council on the Prevention of Deaths of Children and Young People

Associate Professor Colleen Hayward, Member, Directors General Selection Panel Pool of the Commissioner for Public Sector Standards

Jocelyn Jones, NHMRC Indigenous Health Research Panel

Jocelyn Jones, Australian Research Alliance for Children and Youth – Network Advisory Committee

Dr Deborah Lehmann, Data Safety Monitoring Board for the Maternal pneumococcal immunisation study in the Northern Territory ('PneuMum')

Dr Eugen Mattes, Royal Australian College of General Practitioners (RACGP), Examiner for Fellowship Exams

Anne McKenzie, Member, Consumers' Health Forum of Australia (CHF), Canberra. 2002-ongoing

Anne McKenzie, Consumer Representative CHF, Community Quality Use of Medicines Steering committee. 2004-ongoing

Anne McKenzie, Consumer Representative CHF, National Prescribing Service Pharmaceutical Decision Support Working Group. 2005-ongoing

Anne McKenzie, Consumer Representative CHF, Medicines Australia – Code of Conduct Appeals Committee. 2006 -ongoing

Anne McKenzie, Consumer Representative CHF, National E-health Transition Authority (NeHTA) Consumer and Clinical Discussion Forum. 2006 ongoing

Anne McKenzie, Consumer Representative CHF, National Prescribing Service New Drugs Working Group 2006-ongoing

Dr Elizabeth Milne, NHMRC Grant Review Panel Member (2005-6)

Dr Natasha Nassar, Member of Royal Australasian College of Physicians Working Party to update policy statement on Routine circumcision of newborn and infant males

Dr Wendy Oddy, Baby Friendly Hospital Initiative

National Advisory Committee - Invited position 2003-2007.

International

Associate Professor Eve Blair, Editor with responsibility for Cerebral Palsy. Cochrane Review Group for Movement Disorders, Lisbon.

Clinical Professor Carol Bower, Global Burden of Diseases, Risks and Injury Expert Group for Congenital Abnormalities, member 2007 –

Associate Professor Jane Freemantle, Member International Society of Perinatal and Infant Death, Epidemiology Working Group

Associate Professor Jane Freemantle, Member of the International Indigenous Measurement Group

Dr Deborah Lehmann, Member of the Scientific Committee of the 6th International Symposium on Pneumococci and Pneumococcal Diseases, Iceland 2007.

Dr Jianghong Li, Associated Editor (Since 2005), Rural Sociology published by American Rural Sociological Association

Dr Jianghong Li, First Guest Editor, Rural Sociology: A special issue on Social Determinants of Child Health and Wellbeing in Health Sociology Review December 2008

Dr Eugen Mattes, Member of Imprints Center for Genetic and Environmental Lifecourse Studies, Columbia University (2005-)

Dr Eugen Mattes, Member of New York Academy of Sciences (2005 -)

Dr Elizabeth Milne, Member, Working party for the development of international studies of embryonal cancers in children, WHO International Agency for

Research into Cancer, Lyon, France (2006-7)

Dr Elizabeth Milne, Member, Coordinating Committee of the Childhood Leukaemia International Consortium (2006-7)

Dr Wendy Oddy, Treasurer, Local Organising Committee, International Society for Research into Human Milk and Lactation. International conference held in Perth, Western Australia 2004-2008.

Dr Wendy Oddy, Executive Committee Member, International Society for Research into Human Milk and Lactation, 2008-2010.

Dr Wendy Oddy, Member, International Society for Research into Human Milk and Lactation, since 2001.

Invited Presentations

Allen, Byrne, Davis, Zubrick, Eating disorders in a community sample of mothers: Associations with maternal, family, and child factors, Australian and New Zealand Association for Eating Disorders National Conference, 2007

Watt, Byrne, Blair, Davis, Objective and subjective measures of obesity for predicting mental health outcomes in children, Australasian Association for the Study of Obesity, 2007

Allen K, Byrne S, Davis EA., Longitudinal Study of Binge Eating and Eating Disorder Symptoms in Overweight and Obese Children: Findings from the Childhood Growth and Development Study. 10th International Congress on Obesity, Sydney NSW.

Bebbington, A., Downs, J., Leonard, H., Jacoby, P., McIlroy, O., Kaufmann, W.K., Msall, M., Mobility Skills in Rett syndrome as Determined by Video Analysis. Annual

Scientific Meeting of the Royal Australian College of Physicians. Melbourne; May 2007.

Associate Professor Eve Blair, *Reliable descriptions of Cerebral Palsy. PLAN Fund raising dinner. Joondalup Country Club. Mar 22 07.

Associate Professor Eve Blair, Prediction and/or causation. The effects of varying the comparison group: using cerebral palsy and pre-eclampsia as an example. Perth Epidemiology Group. Rottneest Island, May 4/5 07

Associate Professor Eve Blair, *Epidemiology of Cerebral Palsy. 15th Annual Meeting of the Japan Neonatal Follow-up Group, Tokyo, Japan, May 20th 07

Associate Professor Eve Blair, *How CP rates have changed with the development of NICU 1975-99 in Western Australia. Osaka, Japan May 17th 07

Associate Professor Eve Blair, *How CP rates have changed with the development of NICU 1975-99 in Western Australia. Tokyo, Japan May 18th 07

Associate Professor Eve Blair, *An epidemiological understanding of the aetiology of cerebral palsy. Royal Australian and New Zealand College of Obstetrics and Gynecology annual meeting. Oct. 2nd 2007, Brisbane

Bourke, J, Leonard H, Bebbington A, Dyke P, Jacoby P, Aiberti K and Bower, C., The physical and mental health of mothers of children with Down syndrome- what makes a difference? 42nd Australasian ASSID Conference, 2007, Perth.

Bourke, J., The physical and mental health of mothers of children with Down syndrome- what makes a difference? . Telethon Institute for Child Health Research Scientific Meeting (Away Days) March 2007, Perth

Clinical Professor Carol Bower, "Surveys of health

professionals' knowledge and practice regarding fetal alcohol syndrome and alcohol use in pregnancy", at the 2nd International Conference on Fetal Alcohol Spectrum Disorder, Victoria, BC, Canada. March 2007

Clinical Professor Carol Bower, "Health professionals making a difference: Fetal Alcohol Spectrum Disorder, alcohol and substance use in pregnancy, and breastfeeding", in the Westlink Satellite Series, Perth. July, August & September 2007

Clinical Professor Carol Bower, "Folate fortification: what is the evidence, and what should Australia do? Neural tube defects and their prevention with folate", at the Perth Epidemiological Group meeting, Perth. August 2007

Clinical Professor Carol Bower, "A comparison of encephaloceles with other NTDs: trends before and after folate promotion and voluntary food fortification in Western Australia", at the 5th International Neural Tube Defects Conference, Monterey. September 2007

Clinical Professor Carol Bower, "Consumer views on statutory notification to the Western Australian Birth Defects Registry", at the 3rd Scientific Session and Annual Meeting of the ICBDSR. Chianciano, Italy. October 2007

Clinical Professor Carol Bower, "Increasing prevalence of hypospadias in Western, 1980-2000", at the 3rd Scientific Session and Annual Meeting of the ICBDSR, Chianciano, Italy. October 2007

Clinical Professor Carol Bower, "Folate and the prevention of neural tube defects in Australia", at the Developmental Origins of Health and Disease conference, Perth. November 2007

C Shepherd, R Walker, "WAACHS Volume Four

Results", presentation to students at Curtin University's Centre for Aboriginal Studies, May 2007

Colvin C., Using population-based linked data for surveillance of prescribed medication use in pregnancy. Obstetric Drug Information Services Workshop of the Australian Birth Defects Society, Sydney, Australia, May 2007

D'Antoine H, France K, Henley N., Alcohol and pregnancy: health professionals making a difference. Perth, W.A.; May 2007

D'Antoine H, France K., Alcohol and pregnancy. Drug and Alcohol Conference (WA). Perth, W.A.; 2007.

D'Antoine, H. A., FASD in Indigenous Australians. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007, Victoria, BC, Canada

D'Antoine, H. A., Failure to thrive in Aboriginal children. Perth, Western Australia; April 2007.

de Groot J., Case-control study of cerebral palsy in term and preterm infants in Western Australia 1980-1995: Who goes to NICU? Australasian Epidemiological Association. Hobart, Tasmania.; August 2007.

Glenys Dixon, The application of registry based systems in epidemiological methods for global autism surveillance and research. International Meeting for Autism Research (IMFAR). Seattle, Washington. U.S.A.; May 2007.

Glenys Dixon, Western Australian Autism Diagnosticians Forum. June 2007, Perth

Glenys Dixon, The Western Australian Register for Autism Spectrum Disorders. Population Sciences Divisional Seminar June 2007, Perth

Dixon, G.& Glasson, E. , Autism Speaks to the World: International Autism Research Congress. July 2007, Mexico City, Mexico (Poster)

Downs J, Bebbington A, Jian L, Jacoby P, Woodhead H and Leonard H., How likely is a girl with Rett syndrome to fracture and what does this mean? 42nd Australasian ASSID Conference, 2007, Perth.

Paula Dyke, Using the Measure of Processes of Care (MPOC) to measure the family-centred behaviours of services received by families with children with intellectual disability of rare and more common origins. 42nd Australasian ASSID Conference, 2007, Perth.

Tracey-Lee Edwards, "An Indigenous Perspective on Aspiration", presentation to Young Leaders Forum, June 2007

Tracey-Lee Edwards, "Youth Participation", presentation to the Healing Our Spirit Youth Forum, November 2007

Elliot E, Payne J, Morris A, Haan E, Bower C. , Epidemiology of FAS in Australia. 2nd International Conference on Fetal Alcohol Spectrum Disorder. Victoria, B.C. Canada; March 2007.

Elliot E, Payne J, Morris A, Haan E, Bower C. , Fetal Alcohol Syndrome in Australia. Royal Australian College of Physicians Congress. Melbourne; May 2007.

Elizabeth Elliot, Cochrane systematic review of the literature: Interventions for Children with FASD. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007, Victoria, BC, Canada

A Ferrante, Developmental Pathways in WA Children: A holistic approach to inform early intervention strategies. Youth Think Tank, WA Office of Crime and Prevention, Perth, July 2007.

France K, Payne J, Henley N, D'Antoine H, Elliot E, Bower C., Alcohol and pregnancy resources for health professionals: a client's perspective adds value. Public Health Association of Australia 2007: reality Check. Fremantle, W.A. October 2007.

France K, Payne J, Henley N, D'Antoine H, Elliot E, Bower C. , Alcohol and pregnancy resources for health professionals: a client's perspective adds value. People, Places, Priorities. Alice Springs, Northern Territory; September 2007.

Freemantle J, Doyle A, Yarran S, Johnson J, Jones J. , Working with Aboriginal communities to achieve sustainable change in reduction of SIDS Paediatric and child health update. Notre Dame University Fremantle, W.A.; May 2007.

J Hammill, Advocacy for the unborn child. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007, Victoria, BC, Canada

Associate Professor Colleen Hayward, "Act as if This Child Was Yours", presentation to the Ministerial Community Roundtable on Child Protection, March 2007

Associate Professor Colleen Hayward, "Strengthening the Capacity of Aboriginal Children, Families and Communities", presentation to the International Heads of Child Support Agencies Meeting, April 2007

Associate Professor Colleen Hayward, "Human Rights and Indigenous Communities", presentation to NAIDOC Open Forum sponsored by the WA Department of the Attorney General, July 2007

Associate Professor Colleen Hayward, "Dignity, Justice, Rights: Some of the Challenges Facing Indigenous Communities", keynote presentation to the Annual General Meeting of Amnesty International, July 2007

Associate Professor Colleen Hayward, "Building Cultural Security into Health Service Delivery", presentation to the Garma Cultural Festival Key Forum, August 2007

Associate Professor Colleen Hayward, "International Day of Peace: bringing Peace Home", presentation to the Greens' 2007 Bridging Dinner, September 2007

Associate Professor Colleen Hayward, "Indigenous Health and Community Wellbeing", presentation to the Rotary Club of Swan Districts, October 2007

Associate Professor Colleen Hayward, "Women, Mothers and Daughters", keynote presentation to the Women's Council for Domestic and Family Violence 30th Anniversary Dinner, October 2007

Dr Ingrid Laing, Are children in developing countries more genetically susceptible to ALRI's than children in developed countries? Arizona Respiratory Center, Tucson Arizona, USA, Jun 14 2007

Dr Ingrid Laing, Genetics of asthma and allergy – are we getting anywhere? 18th Australasian Society of Clinical Immunology & Allergy Annual Scientific Meeting/ Australasian & South East Asian Tissue Typing Association 31st Annual Scientific Meeting, Fremantle WA, Nov 16 2007

Dr Deborah Lehmann, Otitis Media and the Kalgoorlie Study. Ear Research Symposium, Sir Charles Gairdner Hospital, Perth, WA. Mar 23 2007

Dr Deborah Lehmann, Maternal pneumococcal immunisation in PNG. Indigenous Immunisation Research Workshop, Darwin, NT, Aug 21 2007.

Dr Deborah Lehmann, Upper respiratory carriage of Streptococcus pneumoniae in Aboriginal and non-Aboriginal children in the Kalgoorlie-Boulder area. WA Branch of the Australian Society for Microbiology, Perth,

WA, Dec 4 2007.

Dr Helen Leonard, Rett syndrome: From surveillance to genotype-phenotype correlation. Annual Scientific Meeting of the Royal Australian College of Physicians. Melbourne; May 2007.

Dr Helen Leonard, Australia-China alliance: Investigating the relationship between genotype and phenotype in Rett syndrome. Beijing; September 2007.

Dr Helen Leonard, Clinical variability and relationship with genotype in Rett syndrome: Insights from AussieRett and InterRett. Department of Paediatrics and Adolescent Medicine, University of Hong Kong. Hong Kong; September 2007.

Dr Helen Leonard, Leaving school: Maximizing participation and life outcomes in youth with an intellectual disability transitioning from secondary school to adult life. ARACY Workshop. Perth; November 2007.

Dr Helen Leonard, WA Autism Epidemiology AS-CDC International Autism Epidemiology Network Registry Workgroup Meeting. New York; December 2007.

Dr Helen Leonard, Launch of Down Syndrome NOW Report. Perth; 7 December 2007.

Love S, Williams N, Blair E, Gibson N., The Australian Spasticity Assessment Scale. R&A, PMH, October 19th Perth 07

Dr Elizabeth Milne, National case-control studies of childhood cancer in Australia: overview and update Australian and New Zealand Children's Haematology/ Oncology Group Annual Scientific Meeting, Sydney, May 2007.

Dr Elizabeth Milne, A possible protective effect of maternal folate supplementation on cancer in the

offspring: a case-control study. Nutrition Society of Australia, Perth November 2007.

Dr Elizabeth Milne, The Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children: Study design and Progress Report" Meeting of the Childhood Leukemia International Consortium (CLIC), Los Angeles, USA, April 2007

Nassar N, et al. , Geographical variation of hypospadias in Western Australia. Australasian Epidemiological Association Hobart; August 2007.

Nassar, N., Leonard, H., Blair, E., Bourke, J., Mulroy, S., De Klerk, N., Bower, C. , The relationship between intrauterine growth and subsequent intellectual disability in a ten year population cohort of children in Western Australia. Society for Perinatal and Paediatric Epidemiological Research. Boston; June 2007.

Nassar, N., Leonard, H., Blair, E., Bourke, J., Mulroy, S., De Klerk, N., Bower, C. , The relationship between intrauterine growth and subsequent intellectual disability in a ten year population cohort of children in Western Australia. Australasian Epidemiological Association. Hobart; August 2007.

Dr Wendy Oddy, 2007 Experimental Biology Meeting, American Society of Nutrition Symposium "Breastfeeding and Atopic Disease" Washington DC, USA April 28 – May 2nd 2007.

Dr Wendy Oddy, 5th International Congress on Developmental Origins of Health & Disease, 'The impact of breast milk on long-term child health and development' Perth, Western Australia, 6 – 10 November 2007.

Dr Wendy Oddy, 3rd International Brain Phospholipids conference 2008, "Fatty acids and depression project",

Oslo, Norway September 2008.

Dr Wendy Oddy, Breastfeeding and mental health in a cohort of adolescents in WA. 16th Annual Meeting of the Australasian Epidemiological Association, Hobart, 27-28th August 2007.

Dr Wendy Oddy, Invited lectures 'Nutrition in Pregnancy, Infant and toddler nutrition', Food & Nutrition in Public Health 750.208, School of Pop. Health, University of Western Australia, August 2005, 2006, 2007.

O'Donnell M, Stanley F, The context for child protection: Evidence and research. Ministerial Community Roundtable on Child Protection, Perth, March 2007.

Colleen O'Leary, Alcohol in Australia: The impact on children. Curtin Child and Community Health Nursing Students. Perth; February & November 2007.

Colleen O'Leary, Systematic review of the literature of alcohol exposure during pregnancy and fetal harm. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007, Victoria, BC, Canada

Colleen O'Leary, Australian policy on alcohol use in pregnancy: How it compares with other English speaking countries. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007,

Colleen O'Leary, Trends in mode of delivery 1984-2003. Can they be explained by pregnancy and delivery complications? 16th Australasian Epidemiological Association Conference (AEA). Hobart; August 2007.

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Elizabeth Peadon, International survey of services for the assessment and diagnosis of children with FASD. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007, Victoria, BC, Canada

Elizabeth Peadon, Women's knowledge, attitudes and practice regarding FAS and alcohol use in pregnancy. 2nd International Conference on Fetal Alcohol Spectrum Disorder March 2007, Victoria, BC, Canada

Glenn Pearson, "Rekindling for Whom?", keynote presentation to the Clifford Beers International Mental Health Rekindling the Flame Conference, February 2007

Glenn Pearson, "The Importance of Research in the Design of Parenting Services", presentation to the WA Department for Child Protection's Parenting Services Conference, September 2007

Glenn Pearson, "Towards Egalitarian Research

Relationships with Aboriginal People – an Aboriginal Community Determined Social Research Design”, presentation to the NHMRC National Research Ethics Conference, October 2007

Glenn Pearson, Mental health promotion 2007 and beyond. Clifford Beers Foundation “Kindling the flame: Promoting mental health and wellbeing” conference, Perth, February 2007

Glenn Pearson, Towards egalitarian research relationships with Aboriginal people – An Aboriginal community determined social research design. National Research Ethics Conference, Melbourne, October 2007.

Carrington Shepherd, “WAACHS Volume Three Results”, presentation to the Department of Education and Training’s South-West School Psychologists Conference, January 2007

Carrington Shepherd, “Key Data for Health Professionals – How to Access and Use Them”, presentation to the Rio Tinto Child Health Partnership National Symposium, May 2007

Carrington Shepherd, “Implementing the AEDI Across the Pilbara”, presentation to the Early Childhood Development Forum, October 2007

Silburn SR, Strengthening the capacity of Aboriginal children, families and communities in Geraldton. Geraldton, W.A.; May 2007.

Silburn SR., Supporting children in education: Building capacity across multiple generations. Bunbury, W.A.; June 2007.

Stanley F, Langridge A, Mattes E, Equitable Healthy Development: The Role of Population Data. 5th International Congress on Developmental Origins of Health and Disease, Perth, November 2007.

Associate Professor Kate Taylor, Twins and singletons with Specific Language Impairment. Twins and Child Health Research Conference sponsored by the Australian Twin Register, Western Australian Twin Register, Murdoch Childrens Research Institute and Australian Research Alliance for Children and Youth, Melbourne Victoria (April, 2007).

Associate Professor Kate Taylor, Children at risk for speech and language difficulties in the early years: Who are they and how can we help? Seminar presented to the WA Early Years Strategy State Conference (June, 2007).

Associate Professor Kate Taylor, Specific Language Impairment over time. Seminar presented at the Language Development Centres and Schools of Western Australia Professional Development Meeting, Perth, Western Australia (April, 2007).

Dr Roz Walker, “The Western Australian Aboriginal Child Health Survey: Communicating the Policy Implications and Encouraging their Uptake”, presentation to the ARACY Access Grid Seminar, October 2007

Zubrick SR, Shepherd C., Strengthening the capacity of Aboriginal Children, Families and Communities. Perth; 2007.

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