Research to improve the health and wellbeing of our most important asset – our children

TELETHON INSTITUTE FOR Child Health Research

PREVENTION
INNOVATION
DEDICATION

Annual Report **2008**

Scientific Supplement

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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 improving child health and wellbeing

We are housed in a purpose-built research facility on the edge of the Perth CBD and have close to 470 staff and students as well as around 80 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.

The Institute is headed by Professor Fiona Stanley AC who was named 2003 Australian of the Year for her commitment to improving the health and wellbeing of Australia's young people.

What we do

Our focus is on children, young people and their families and the environments in which they live.

Our research priorities are focused on the most complex, costly and devastating health problems facing our children in the 21st century.

We have a firm commitment to promoting evidence-based action and preventative strategies.

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.

Division of Cell Biology

The research focus in the Division of Cell Biology continues to be upon the cellular and molecular mechanisms underlying susceptibility and resistance to infections and allergic diseases in the respiratory tract during childhood. Earlier work from the Division has established the important paradigm that risk for postnatal development of atopy and asthma 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 later 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 remains 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. An important complementary stream of research in our Division is aimed at elucidating 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 determining the role of these cells as determinants of susceptibility to atopy/ airway hyper-responsiveness in "high risk" strains of rats. We have also developed a program on 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 and allergy study

EM Hollams, M Serralha, BJ Holt, FT Parsons, B Zhang and PG Holt in collaboration with N de Klerk, Biostatistics TICHR and PD Sly, Clinical Sciences TICHR

In 2007 we completed ***in vitro*** analyses and data collection for the 14 year old follow-up of the W.A. Pregnancy Cohort, which has been followed intensively since birth and detailed statistical analyses on these data have been ongoing throughout 2008. We collected data covering four broad areas: clinical history, genotypic information on a large panel of atopy/asthma candidate genes, lung physiology and immunology. Within the 1,380 cohort members studied 827 subjects were atopic (as determined by IgE measurement), 140 were asthmatic, and 81% of asthmatics were also atopic. The most common allergic sensitisation was to house dust mite (HDM), which was seen in 39% of the total cohort and 66% of asthmatics. HDM-specific IgE contributed strongly to asthma risk; subjects with the highest levels of HDM-IgE were at highest risk of asthma and also bronchial hyperreactivity, a respiratory condition associated with asthma. Amongst subjects sensitised to HDM, biomarkers increasing the risk for asthma in addition to HDM-IgE were a positive family history of atopy, increased levels of eosinophil activation, increased degree of bronchial hyperresponsiveness, high levels of adaptive immune function (mitogen-induced IFNγ and IL-10), and reduced innate immune responsiveness (lipopolysaccharide-induced IL-12). Increased asthma severity amongst HDM-sensitised subjects was related to a similar set of risk factors. Our findings overall suggest that asthma in teenagers is predominantly driven by atopy which can act directly to cause airways inflammation, or indirectly to create susceptibility to other inflammatory (but atopy independent) mechanisms.

This research is funded by the National Health & Medical Research Council of Australia and the Stanley Trust, UK.

Relationship of S. aureus enterotoxin exposure to risk of allergic and respiratory disorders

EM Hollams, FT Parsons, BJ Holt, B Zhang and PG Holt in collaboration with PD Sly, Clinical Sciences TICH and C Bachert, Ghent, Belgium.

Staphylococcus aureus is a commensal bacterium carried by at least 25% of the population in the nose, and which can produce several enterotoxins that behave as superantigens, the most powerful known T-cell stimulants. A growing body of evidence suggests these superantigens are involved in airway disease, mediated at least in part by sensitisation to ***S. aureus*** and production of ***S. aureus*** enterotoxin-specific IgE (SAE-IgE). We measured SAE-IgE in all 1,380 14 year olds of the WAPC cohort to determine whether sensitisation to ***S. aureus*** enterotoxin is more prevalent amongst teenagers with asthma, rhinoconjunctivitis, eczema, wheeze, exercise-induced wheeze or bronchial hyperreactivity. Sensitisation to ***S. aureus*** enterotoxin was more prevalent amongst symptomatic groups for all clinical outcomes examined except for eczema. When examined as the sole risk factor, increased SAE-IgE levels predicted all outcomes examined except for eczema and rhinoconjunctivitis, and were associated with increased asthma severity. In particular, SAE-IgE significantly increased risk of non-atopic bronchial hyperresponsiveness. We also measured in vitro immune responses to ***S. aureus*** enterotoxin B within the whole cohort to examine whether allergic or respiratory disorders were associated with hyperresponsiveness. ***S. aureus*** enterotoxin B-induced hyperproduction of IL-5, and to a lesser extent IL-13, was associated with asthma, bronchial hyperresponsiveness and other respiratory disorders. S. aureus enterotoxin B-induced IL-5 was a significant risk factor for atopic bronchial hyperresponsiveness. Our results suggest that exposure to ***S. aureus*** enterotoxins exacerbate bronchial hyperresponsiveness and atopic asthma in teenagers, and reduction or prevention of ***S. aureus*** carriage may represent a complementary approach for treatment of respiratory disorders in this group.

This research is funded by the National Health & Medical Research Council of Australia and the Stanley Trust, UK.

Examination of seasonal allergic responses and rhinoconjunctivitis etiology

EM Hollams, M Serralha, BJ Holt, FT Parsons, B Zhang and PG Holt in collaboration with N de Klerk, Biostatistics TICHR and PD Sly, Clinical Sciences TICHR

We are also studying the aetiology of allergic rhinoconjunctivitis in the WAPC cohort of 14 year olds. Ryegrass pollen is a seasonal allergen that plays a role in the exacerbation of atopic conditions such as rhinoconjunctivitis and asthma, as does the perennial allergen house dust mite which is constitutively present throughout the year. Rhinoconjunctivitis is itself a risk factor for asthma severity in this cohort, as our results above describe; 38% of the cohort had rhinoconjunctivitis, and the majority of asthmatics had

rhinoconjunctivitis (97/140: 69%). In addition to measuring HDM-induced cytokines, as outlined above, we have measured in vitro immune responses to Rye grass pollen within the whole cohort. When Rye-sensitised subjects were stimulated in vitro with Rye, those with rhinoconjunctivitis produced higher levels of the Th2 cytokines IL-4, IL-5, IL-9, and IL-13, in addition to the Th1 cytokine IFNγ, than those without rhinoconjunctivitis; levels of IL-10 did not differ. Blood used for in vitro immune response measurement was collected across the seasons over a three year period. This allows us to investigate the hypothesis that Rye-sensitised subjects who are bled out of Rye season will not show a response to Rye unless they are also sensitised to a perennial allergen such as house dust mite. These analyses are ongoing.

This research is funded by the National Health & Medical Research Council of Australia and the Stanley Trust, UK.

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

We initiated a multicentre clinical trial in July 2006 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 and USA (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 three year follow-up period by 50%. 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 in Australia and the US through the full 12 months of treatment with active or placebo and have established safety. The funding body (ITN) has decided to limit enrollment in this trial to the first 50, who will now be followed through until three years post-cessation of treatment. Further funding to increase recruitment will be considered if we can demonstrate significant reduction in asthma/allergy in the 25 treated subjects. These results will be available some time in 2011.

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

Identification of novel genes associated with allergen-driven Th2 responses

KL McKenna, A Bosco, PD Sly, PG Holt

This study aims at identifying new genes which drive the allergic T-cell memory response in humans. Employing microarray technology, we have discovered a large panel of genes induced in CD4+ T-cells following house dust mite (HDM) stimulation in atopic subjects compared to non-atopic subjects, beyond the well characterised Th2 cytokine gene signature that includes IL-4, IL-5, IL-9 and IL-13. Kinetic studies revealed a cluster of novel genes which peaked early following HDM stimulation and were co-expressed with IL-4 and IL-4 receptor. Many of these novel genes are thought to play a role in cell signalling. A second cluster, which peaked late in the response, contained classical Th2 effector cytokines as well as other effector molecules. The preferential expression of the novel Th2-associated genes in atopics was confirmed by quantitative RT-PCR in at least two additional patient populations. Functional experiments demonstrated that many of the novel genes are regulated by the archetypal Th2 cytokine IL-4, or IL-2, which drives T-cell proliferation. Furthermore, expression of the novel genes could be prevented by blocking the IL-4 and IL-2 pathways with antibodies to their receptors. Further investigation involving separation of individual CD4+ T-cell subsets revealed that the Th2-associated genes partition at different stages of Th-memory cell differentiation. In particular a discrete gene signature defines the "effector" T-memory cell compartment in atopics and encompasses the bulk of potentially toxic cytokines that are likely to drive airways inflammation, as well as some novel "amplifier" genes that represent potential asthma drug targets. Future

experiments will delve into the role these novel genes play in driving the Th2 inflammatory cascade, and utilise siRNA technology to selectively silence of one or more novel genes in an attempt to attenuate the Th2 immune response in atopics.

Airway epithelial cells and regulation of dendritic cell function

A Rate, JW Upham and PG Holt

Atopic asthma pathogenesis is driven by the combined effects of airway inflammation generated during responses to viral infections and aeroallergens, and both these pathways are regulated by dendritic cells (DC) that differentiate locally from monocytic precursors. These DC normally exhibit a sentinel phenotype characterised by active antigen sampling but attenuated presentation capability, which limits the intensity of local expression of adaptive immunity. How this tight control of airway DC functions is normally maintained and why it breaks down in some atopics leading to immunopathological changes in airway tissues, is unknown. We postulated that signals from adjacent airway epithelial cells (AEC) contribute to regulation of local differentiation of DC. We tested this in a co-culture model containing both cell types in a GM-CSF/IL-4-enriched cytokine milieu characteristic of the atopic asthmatic airway mucosa. We demonstrate that contact with AEC during DC differentiation up-regulates expression of the function-associated markers MHC II, CD40, CD80, TLR3 and TLR4 on DC with concomitant up-regulation of antigen uptake/processing. Moreover, the AEC-conditioned DC displayed increased LPS responsiveness evidenced by higher production of IL-12, IL-6, IL-10 and TNF-α. The Th2-memory activating properties of AEC-conditioned DC were also selectively attenuated. Data from microarray and blocking experiments implicates AEC-derived type-1-interferons and interleukin-6 in modulation of DC differentiation. Collectively these findings suggest that resting AEC modulate local DC differentiation to optimise antimicrobial defences in the airways and in the process down-modulate capacity for expression of potentially damaging Th2 immunity.

This research is funded by the National Health & Medical Research Council of Australia, The Asthma Foundation of Western Australia and the Stan&Jean Perron Trust.

Vaccine Studies

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), P Richmond (UWA School of Paediatrics and Child Health), and 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 and invasive pneumococcal disease. Accelerated immunization schedules, including neonatal vaccination, should therefore be considered in these high risk populations to induce the earliest possible protection. To prove the safety and immunological feasibility of neonatal vaccination with a 7-valent pneumococcal conjugate vaccine (7vPCV), 318 newborns have been enrolled and randomised to receive 7vPCV either at (1) birth, one month and two month (neonatal group), (2) one month, two month and three month (infant group) or (3) receive only routine immunizations (control group) in our trial in PNG. For a period of 18 months the children are being followed for their development of cellular and humoral immune responses, bacterial upper respiratory tract carriage and morbidity. In 2008, all children completed their nine-month follow up. We showed that at three months of age, neonatal 7vPCV priming (followed by a dose at one and two months) was associated with enhanced Th2, but not Th1, cytokine responses to the vaccine protein carrier CRM197 relative to 7vPCV at one and two months only. T-cell responses to other vaccine antigens were similar in all groups, but TLR-mediated IL-6 and IL-10 responses were enhanced in 7vPCV-vaccinated compared to controls. Children experienced few local side effects to 7vPCV vaccination (5.4%) and few systemic side effects following any vaccination between birth and three months (7.4%). Reactions predominantly involved tenderness of the vaccination site. These first immunological outcomes indicate that neonatal and infant immunization with PCV is safe and immunogenic in PNG. The potential implications of these skewed Th2 and innate immune responses on subsequent immune responses up to age 18 months are the subject of ongoing studies.

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

Immune ontogeny in infants in the developing and developed world

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

There is increasing evidence that the functional state of the immune system at birth is predictive of the kinetics of immune maturation in early infancy. This maturation process has a major impact on early vaccine responses and is a key determinant of risk for communicable and non-communicable diseases in later life. In this study we test the hypothesis that environmental and genetic factors that are typical for resource-poor populations can modulate neonatal immune function and hence influence disease risks and vaccine responses in infancy. Hereto we are collecting cord blood mononuclear cells from births in two areas of Papua New Guinea (PNG), one in the coastal area of Madang that experiences a year round transmission of malaria, and the other in Goroka, in the Highlands. Detailed information on risk factors including malarial and helminth infections and exposure to indoor air pollution during pregnancy is being collected. In our preliminary studies we have identified major differences in Toll-like receptor (TLR)-mediated innate immune responses, and function of antigen presenting cells, T helper cells, and possibly regulatory T-cells between CBMC of PNG newborns and CBMC collected from births in the metropolitan area of Western Australia. These discrepancies, including differences within the PNG study population based on risk exposure, will be further addressed in our ongoing studies.

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

Variation between populations in neonatal innate cytokine responses to Bacillus Calmette-Guerin

AHJ van den Biggelaar, MA Nadal-Sims, C Devitt and PG Holt in collaboration with SL Prescott (UWA School of Paediatrics and Child Health) and P Siba (Papua New Guinea Institute of Medical Research)

Infants in low-income countries are vaccinated with ***Mycobacterium bovis*** bacillus Calmette-Guerin (BCG), preferably within the first month of life, but its efficacy varies between populations. Moreover, some studies suggest that BCG can protect against the development of atopic disease, but this allergo-protective effects of BCG seems to be more evident in children from low-income countries and less so in children from high-income countries. We hypothesized that differences between populations in neonatal immune responses may explain these discrepancies, and tested this by studying BCG-related neonatal innate immune responses in cord blood mononuclear cells (CBMC) from children born in a high-income ([Western] Australia, WA) versus low-income country (Papua New Guinea, PNG). We showed that BCG-induced IL-10 and IFN- responses were significantly higher in CBMC of PNG newborns and promoted the subsequent development of PPD-memory T helper 2 responses in infancy. When primed with IFN- , the production of BCG-induced pro-inflammatory cytokines (including TNF-α, IL-12p70, but in particular IFN-) was enhanced to a significantly higher extent in WA than in PNG newborns. Moreover, NK-cells of WA newborns produced IFN- in response to IFN- priming and BCG stimulation, whereas NK-cells of PNG newborns contributed only indirectly to this response. These data show that BCG-related neonatal innate immune responses influencing the development of T helper cell responses in early infancy differ between children born in a resource-poor versus high-income country. This may affect resistance to ***M. tuberculosis*** infections and the risk for atopic disease in later life.

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

Neonatal Pertussis Vaccination

O White, J Rowe and P G Holt in collaboration with P Richmond, School of Pediatrics and Child Health, UWA and P McIntyre, National Centre for Immunization Research and Surveillance, Sydney.

Severe Whooping Cough (pertussis) is most common in newborn babies, who are too young to have received pertussis vaccination, which is first given at two months of age. 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 76 children following the standard vaccine schedule (vaccine administered at two, four and six months of age) either alone, or together with an additional vaccine dose given at birth. Blood was collected at birth, and at two, four, six and eight months of age. Our data provide evidence that neonatal pertussis vaccination induces significantly

higher levels of vaccine-specific IgG antibody as early as two months of age compared to those vaccinated according to the current schedule. At eight months of age, the levels of vaccine-specific IgG were similar in all three groups. In a subgroup of 30 subjects studied for cell-mediated immune memory, 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 was collected from these children at two years of age. Cell-mediated immunity has been measured in the 27 available subjects and the results are currently being analysed.

DTaP Preschool Trial

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

The DTaP Preschool Clinical Trial aims to investigate the effects of the removal of the 18-month dose of DTaP vaccine on the persistence of vaccine-specific memory and the incidence of local reactions following the pre-school dose. Recruitment to the clinical trial closed in 2008 with 104 subjects recruited, and 99 available for study. Currently, final follow-up appointments are underway and are due to be completed by October 2009. The rates of large local reactions to the preschool booster dose in trial subjects, who did not receive a DTaP dose at 18-months, is significantly less than in subjects of a previous trial, who did receive an 18-month dose (12% and 43% respectively). Vaccine-specific humoral responses were measured from blood samples collected before and four to six weeks after the preschool booster DTaP vaccination. After the preschool dose, all subjects had protective levels of antibody against diphtheria and tetanus. However, in the pre-vaccination samples, a proportion of subjects had vaccine-specific antibody titres below the protective level. This is possibly due to the absence of a booster dose at 18 months. To determine the effect of the removal of the 18-month dose on vaccine-specific memory, cell-mediated immunity will be examined in 2009. In addition, micro-array technology will be used to gain further insights into the cell-mediated pathway of immune memory and the inflammation associated with the large local reactions.

Animal Model Studies

Rat model of allergic airways inflammation

We have developed a unique rat model to probe the mechanisms underlying the return to, and maintenance of "normal" function in the airways following an asthma exacerbation. Our model features two inbred rat strains, which closely approximate human "high allergy risk - HR" and "low allergy risk - LR" phenotypes. We have demonstrated that sensitised LR rats have the ability to self-regulate the response to aeroallergen challenge via the induction of a regulatory network involving interactions between specific cell types within the airway microenvironment (dendritic cells and T-cell subsets), which operates to efficiently control the intensity and duration of allergic airways responses. In contrast, our ongoing studies suggest disruption of these regulatory mechanisms in sensitised HR rats, such that the outcome of aeroallergen challenge is a more severe and persistent form of inflammatory airways disease with continuing airways hyperresponsiveness (AHR- a hallmark of the human atopic asthmatic response). Our data has developed the concept that in HR rats there is an association between the development of persistent AHR and a reduced number of cells capable of regulating the inflammatory airways response within the airway mucosa. Moreover, our preliminary experimental data suggests a series of abnormalities in the functions of these regulatory that are responsible for controlling an asthma exacerbation, and further that these abnormalities are restricted to respiratory tissues, as the functions of the same cells once removed from the local tissue microenvironment, appear normal. These preliminary findings suggest that "site specific" factor(s) related to the airway mucosa may ultimately determine whether allergic individuals mount an asthmatic response to aerosol allergen exposure. The "site specific failure of regulation" concept underpinning these experimental model studies, if it can be validated and elucidated mechanistically, offers exciting new possibilities for drug development for asthma treatment, and this represents the long-term aim of our research program.

OM PHARMA collaboration

Regulatory T-cell (Treg) populations are central to the regulatory network that operates in the airways to maintain "normal" respiratory function and control asthma exacerbations. Recent findings in the experimental probiotic literature have suggested that local gastrointestinal tract (GIT) as well as systemic levels of certain types of Treg activity may in some situations be "boosted" by oral administration of microbial stimuli. In these studies we are investigating the applicability of these findings to the control of allergic airways inflammation. In an ongoing collaboration with OM Pharma (Geneva) we have employed a microbial extract, which has previously been tested in

immunocompromised humans with some success in relation to control of infectious and inflammatory diseases in the respiratory tract, as a treatment protocol in our rat asthma model. We have demonstrated that repeated feeding of normal rats with this bacterial extract can indeed boost systemic numbers of certain Treg populations, which results in an effective doubling of baseline numbers within airway mucosal tissues of normal LR rats. If treatment is carried out in sensitised LR animals prior to aeroallergen challenge (i.e. in animals with "pre-boosted" airway regulatory cell compartment defences) the magnitude of the resulting lung inflammatory response and the duration of ensuing airways hyperresponsiveness (AHR) is markedly attenuated. This establishes the principles that this particular subset of Treg can potentially contribute to "normal" airway function and that generation of these in the GIT represents a possible therapeutic target in relation to asthma. These findings will be followed up in our rat model focusing on differences between HR and LR phenotypes.

Regulation of airborne allergen uptake and processing by subsets of airway mucosal dendritic cells (AMDC) during attenuation of AAI

J. Burchell, M. Wikstrom, D. Strickland, V. Fear, P. Sly and P. Stumbles

Following from our publication in this area (von Garnier et al). Allergic airways disease develops after an increase in allergen capture and processing in the airway mucosa (J Immunol. 2007), we have extended this model to examine the role of AMDC in the down-regulation phase of AAI that occurs following chronic exposure to allergen aerosol. We have found that following an initial increase in antigen capture activity during the acute phase, AMDC shut down their allergen capture capacity, coinciding with an decrease in antigen presentation to CD4+ T-cells in vivo in airways and lymph nodes and an increase in functionally active regulatory T-cells in both these sites (Burchell et al). Attenuation of allergen-induced Airway Hyperresponsiveness is mediated by airway regulatory T-cells. Am J Physiol Lung Cell Mol Physiol. 2008.). We are currently investigating this response in more detail, with emphasis on the regulation of CD4 T-cell differentiation and T reg generation by these "tolerised" AMDC.

This research is funded by the National Health & Medical Research Council of Australia and the Asthma Foundation of Western Australia

The timing and longevity of interactions between AMDC and allergen-specific CD4+ T-cells in draining lymph nodes following inhaled antigen challenge

M. Wikstrom, D. Strickland, P. Holt and P. Stumbles

Progress in this area has focussed on the persistence of antigen in draining lymph nodes and how this relates to generation of activated allergen-specific CD4+ T-cells that have the capacity to home to the airways and lung tissue. We have found that early antigen arriving in the lymph nodes within 1 day of delivery to the airways effectively generates lung-homing T-cells in large numbers. However, as the antigen persists there a time-dependent decrease in T-cell recirculation to the lung and in T-cell effector function that is associated with a decrease in the activation status of lymph node DC populations. This work has recently been submitted (Feb, 2009) to the Journal of Immunology. Continuing work in this area will examine the requirement for continued migration of AMDC to the lymph nodes in order to effectively generate lung-homing, pro-allergic CD4+ T-cells, as well as the role that AMDC subsets play in this process.

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

Generation of lung-homing Th2 cells in response to inhaled allergen

K. Wiqvist, M. Wikstrom, D. Strickland, P. Holt and P. Stumbles

We have been using an ovalbumin (OVA) transgenic mouse model to study the kinetics of chemokine receptor (CCR) expression by antigen-experienced CD4+ T-cell populations in the lung in response to a single dose of per nasal (p.n.) OVA. In comparison to naïve T-cells in lung tissue or antigen-specific CD4+ T-cells in lymphoid tissues, antigen-experienced T-cells in lung tissue expressed increasingly higher levels of Ccr1, Ccr2, Ccr3, Ccr4, Ccr5, Ccr8, Cx3cr1, Cxcr3, Cxcr4, Cxcr6 and Cmklr1 mRNA from three through to ten days following p.n. OVA delivery. The elevated expression levels of CCR4 and CCR8 mRNA were confirmed at the protein level by flow cytometry, although the correlation between mRNA and protein expression was variable. The restricted nature of enhanced expression of CCRs to lung-homing, antigen-experienced CD4+ T-cells early after inhaled antigen exposure suggests a primary role for these CCR in the homing of antigen specific T-cells into the respiratory tract and may play a role in recruiting and/or promoting Th2 cell activity during the early stages of allergic airways inflammation. This work will form the basis of a PhD program (K. Wiqvist).

This research is funded by the National Health & Medical Research Council of Australia and a Murdoch University Postgraduate Award.

Staff and Students

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Research Support

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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.

Invited Presentations 2008

Patrick Holt, Plenary Speaker: Strategies to stop the atopic march – American Academy of Allergy, Asthma and Immunology Congress, Philadephia, 2008

Patrick Holt, Symposium Speaker: A multiplex perspective of the immune response in allergy: Risk factors for atopic asthma amongst teenagers – European Academy of Allergy and Clinical Immunology, Barcelona, 2008

Patrick Holt, Plenary Chair: Prevention of Allergic Diseases, European Academy of Allergy and Clinical Immunology, Barcelona, 2008

Patrick Holt, Plenary Speaker: Current state and future perspectives of prophylactic allergen vaccination – 12th International Paul Ehrlich Seminar, Bad-Homburg, 2008

Patrick Holt, Plenary Lecture: Primary prevention of allergy by early intervention with SIT – 7th Symposium on Specific Allergy, Copenhagen, 2008

Patrick Holt, Symposium/Debate: Bystander effects of specific allergen immunotherapy – 7th Symposium on Specific Allergy, Copenhagen, 2008

Patrick Holt, Plenary Speaker: Protection against common respiratory pathogens in early infancy: risks and opportunities – Modern Mucosal Vaccines: Adjuvants and Microbicides, Opporto, 2008

Patrick Holt, Pediatric Pulmonary, James Whitcomb Riley Hospital for Children, Indianopolis, (2008) (Prof. R. Teper): Atopic asthma in children – insight from both cohort studies.

Patrick Holt, Phadia AB, Uppsala, 2008 (Prof. S. Ahlstedt): Genetic markers of atopic asthma susceptibility.

Patrick Holt, Pfizer Pharmaceuticals, Sandwich, 2008 (Dr. B. Champion): Paediatric vaccinology – opportunities and challenges.

Patrick Holt, Glasko Smith Klyne Pharmaceuticals, Stevenage 2008 (Dr. D. Myles): Asthma pathogenesis

Patrick Holt, Medimmune, Cambridge, 2008 (Dr. M. McHale): Aetiology and

pathogenesis of asthma.

Patrick Holt, OM Pharma, Geneva, 2008 (Dr. C Chiquarolli): Modulation of the asthma LPR via oral immunostimulation.

Patrick Holt, Novartis, Horhsam, 2008 (Dr. J. Canvin): Interactions between atopic and viral infections during acute asthma exacerbations.

Patrick Holt, Department of Pulmonology, Inselspital, Berne 2008 (Dr. C. Von Garnier): Asthma pathogenesis in childhood – the role of viral infection

Olivia White, Immune responses in infants to acellular pertussis vaccine administered at birth. 7th Louis Pasteur Conference on Infectious Diseases, Institut Pasteur, Paris 11th-13th November 2008 (Poster presentation).

Olivia White, Effect of the removal of the 18 month DTaP booster vaccine on antibody titres and injection site reactions following administration of the 4 year old booster vaccine. 7th Louis Pasteur Conference on Infectious Diseases, Institut Pasteur, Paris 11th-13th November 2008 (Poster).

Olivia White, Immune responses to neonatal and preschool pertussis vaccination. Department of Immune Regulation and Vaccinology, Institut Pasteur, Paris, 14th November 2008.

Olivia White,Cellular immune responses in infants to acellular pertussis vaccination at birth. Australasian Vaccines and Immunotherapeutics Development Conference, Gold Coast 14th-16th May 2008.

Olivia White, Immune responses in infants to acellular pertussis vaccine administered at birth. Perth Immunology Group (WA Branch of Australasian Society for Immunology) Meeting, Nedlands, 9th-10th October 2008.

Olivia White, Immune responses in infants to acellular pertussis vaccine administered at birth. Princess Margaret Hospital Research & Advances Seminars15th-17th October 2008.

Olivia White, Whooping cough in newborns: a neonatal pertussis immunisation strategy. Infectious Diseases Breakfast Meeting, Telethon Institute for Child Health Research 1st May 2008.

Olivia White, Cellular immune responses in infants to acellular pertussis vaccination at birth. WA Branch Australian Society for Medical Research Conference, 4th June 2008.

Olivia White, Cellular immune responses in infants to acellular pertussis vaccination at birth. Combined Biological Sciences Meeting, University Club, UWA, 29th August 2008 (Poster presentation).

Deborah Strickland, ASI seminar series, invited speaker, Perth, Western Australia, August 2008

Deborah Strickland, 10th International Symposium on Dendritic cells, poster session, Kobi, Japan, 2008

Deborah Strickland, Perth Immunology Group (PIG) symposium, Panel member, Perth, Western Australia, October 2008

Deborah Strickland, ASI annual Symposium, poster session (2), Canberra, Australia, 2008

Anita van den Biggelaar, Invited speaker, Host factors that influence vaccine responses, Xth International Symposium on Respiratory Viral Infections, Singapore, 28 Feb-2 March, 2008.

Anita van den Biggelarr, Invited Speaker, Neonatal Immunisation with Pneumococcal Conjugate Vaccine in Papua New Guinea, PICTURE, Menzies School of Health Research, Darwin, 29 August 2008.

Poster presentations (6), 6th International Symposium on Pneumococci and Pneumococcal Diseases, Reykjavik, Iceland, 8-12 June a.o.

'Vigorous T helper 1 and 2 responses to the 7-valent pneumococcal conjugate vaccine given to Papua New Guinean neonates and young infants'. Anita. H.J. van den Biggelaar, William Pomat, Catherine Devitt, Marie Nadal-Sims, Suparat Phuanukoonnon, Peter Richmond, Peter Siba, Deborah Lehmann, Patrick G. Holt.

Reactogenicity to 7-valent pneumococcal conjugate vaccine given to Papua New Guinean neonates and young infants'. Anita H.J. van den Biggelaar, Suparat Phuanukoonnon, William Pomat, Christine Opa, Pioto Namuigi, Gerard Saleu, Agnes Javati, Albert Sie, Birinu Nivio, Peter Richmond, and Deborah Lehmann

'Maternal and neonatal antibody responses to pneumolysin in relation to early upper respiratory tract carriage of Streptococcus pneumoniae in infants in Papua New Guinea'. Jacinta P. Francis, Peter Richmond, Suparat Phuanukoonnon, Peter Siba, Susan Prescott, Jan Nelson, Helen Keno, Audrey Michael, Deborah Lehmann, Anita H.J. van den Biggelaar

'Effect of neonatal and early immunization with theptavalent pneumococcal conjugate vaccine on morbidity and pneumonia in Papua New Guinea'. Peter Richmond, Suparat Phuanukoonnon, Peter Jacoby, Christine Opa, Pioto Namuigi, Gerard Saleu, Agnes Javati, Birinu Nivion, Anita van den Biggelaar, Peter Siba, Deborah Lehmann.

'Immunogenicity of neonatal pneumococcal conjugate vaccine in neonates and young infants in Papua New Guinea'. William Pomat, Suparat Phuanukoonnon, Anita van den Bigelaar, Annemarie Laumaea, Tilda Orami, Peter Jacoby, Patrick Holt, Peter Siba, Deborah Lehmann and Peter Richmond

'Cellular immune responses to

pneumococcal proteins in children with severe and recurrent Acute Otitis Media'. Selma Wiertsema, Eva Mowe, Ruth Thornton, Shyan Vijayasekaran, Anita van den Biggelaar, Harvey Coates and Peter Richmond

Poster presentation, Toll, Recent Advances in Pattern Recognition, Lisbon, Portugal, 24-27 September, 2008.

'BCG induced innate cytokine responses differ between Papua New Guinean and Australian newborns'. Anita H. J. van den Biggelaar, Marjut Roponen, Marie A. Nadal-Sims, Catherine J. Devitt, Suparat Phuanukoonnon, William Pomat, Meri K. Tulic, Peter Siba, Deborah Lehmann, Peter C. Richmond, Susan L. Prescott, and Patrick G. Holt.

Division of Children's Leukaemia and Cancer Research

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

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

Gene signatures in acute lymphoblastic leukaemia provide insight into the role of the bone marrow microenvironment in leukaemia

Y Tesfai and UR Kees, in collaboration with MJ Firth, RA O'Leary and KW Carter, Division of Biostatistics and Genetic Epidemiology.

The initiating genetic events leading to the onset of acute lymphoblastic leukaemia (ALL) have been extensively characterized, however, the subsequent hits and altered gene expression that facilitate the pathogenesis of ALL are not fully understood. To identify critical genes we performed a genome-wide expression analysis of paediatric B-precursor (pre-B) ALL and compared the profiles to normal CD34+ cells. The investigation of 198 ALL patient specimens from three independent cohorts demonstrated that the majority of genes deregulated in pre-B ALL play a role in cell-cell and extracellular matrix-cell interactions. These findings were corroborated by evidence of the hallmarks of cancer being present in ALL. We identified principal regulatory pathways of B lymphocyte development to be critically affected, and we recorded distinct differences among the cytogenetic subgroups of pre-B ALL. These results suggest that the bone

marrow microenvironment and pathways regulating B cell development contribute to the pathogenesis of pre-B ALL. The biologic insights gained from this study provide novel perspectives for improving treatment strategies for ALL patients.

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

The role of ***CTGF*** in paediatric acute lymphoblastic leukaemia

UR Kees, J Ford and M Welch in collaboration with MJ Firth, Division of Biostatistics and Genetic Epidemiology, and DR Brigstock of the Pediatric Surgery Research Laboratory, Children's Research Institute, Columbus, Ohio, USA.

Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children. It is a heterogenous disease, initiated by a range of genetic events that give rise to multiple clinical subtypes with varying prognoses. Although survival rates are approaching 85%, a significant number of patients continue to relapse and the outlook for these is dismal. In order to improve outcome novel therapeutic strategies are required. Leukaemias arise in the haemopoietic cells of the bone marrow and this microenvironment plays a major role in the disease. Using microarray technology we compared the gene expression profile of ALL to normal $CD34^+$ cells separated from bone marrow, and we identified a set of highly differentially expressed genes. Many of the top-ranked genes are known to mediate cell-cell interactions, including ***ECM1, EFNB2, BMP2*** and ***CTGF***. Four independent studies on B-lineage ALL in paediatric and adult patients showed that 75% of specimens consistently expressed ***CTGF*** at very high levels. In our paediatric patient specimens the gene was expressed over a wide range, from 2.3- to 380-fold by array measurement. Our current studies focus on the mechanisms leading to high ***CTGF*** expression. In order to gain insight into the role of ***CTGF*** in leukaemia we studied ALL cell lines established from paediatric patients and demonstrated secreted CTGF of 30 kDa and 38 kDa, however the proliferation of ALL cells was not enhanced in the presence of recombinant human (rh) CTGF. In contrast, bone marrow stromal cells showed a dose-dependent proliferative response to rhCTGF, suggesting that a paracrine mechanism may be involved. We examined the gene expression of bone marrow stromal cells incubated with rhCTGF and identified prominent signatures implicated in the regulation of cell-cell interactions and proliferation. In order to test strong adhesion (against gravity) we designed a closed culture system and monitored adhesion by flow cytometry under various experimental conditions. The presence of rhCTGF mediated enhanced adhesion of ALL cells. Our current studies focus on the functional role of the signalling molecules implicated by our studies, including resistance to drug therapy. Activation and secretion of CTGF play a prominent role in ALL, leading to modified interactions with the microenvironment, and these processes are thought to promote the growth of pre-leukaemic cells. Improved understanding of the CTGF-mediated changes in pre-malignant and malignant cells in the bone marrow microenvironment is expected to lead to better therapeutic strategies for patients with ALL.

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

Outcome prediction of paediatric patients with acute T-cell lymphoblastic leukaemia (T-ALL) at diagnosis

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

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. In contrast to precursor B-lineage (pre-B ALL), karyotypic abnormalities are not informative for outcome prediction in T-ALL patients. In this study we aimed to identify gene expression profiles (GEPs) with predictive value using microarray technology, allowing us to evaluate the expression of thousands of genes with small amounts of patient material. We studied a cohort of 50 T-ALL patients who were all treated on the same COG-1961 therapy protocol; 28 achieved complete clinical remission while 22 later relapsed. The GEPs for the diagnosis specimens of these patients were generated using the HG-U133 Plus 2.0 microarrays (54,657 probe sets). We were able to identify two risk indexes, RI-M1 (4 genes) and RI-M2 (3 genes measured by qRT-PCR), which predicted outcome with 92% accuracy and with 90% accuracy, respectively. The prediction accuracy of the 3 genes measured by qRT-PCR was determined in an independent validation cohort of 34 T-ALL patients who were treated on similar therapy protocols and this achieved a prediction accuracy of 90%. Similarly, a prediction accuracy of 93% was achieved in an independent patient cohort of 50 patients treated on POG protocols. To gain insight into the biology

of diagnosis specimens from patients who ultimately relapsed, we examined the expression signatures and identified three biological pathways, including cell adhesion receptor activity. These findings warrant further verification in larger patient cohorts.

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

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, RA O'Leary and NH de Klerk, Biostatistics and Genetic Epidemiology.

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, Australia and the Children's Leukaemia and Cancer Research Foundation, WA.

Glucocorticoid resistance in T-lineage acute lymphoblastic leukaemia is associated with a proliferative metabolism

AH Beesley, J Ford, RE Weller, JR Freitas, KU Perera and UR Kees, in collaboration with MJ Firth, Division of Biostatistics and Genetic Epidemiology.

Glucocorticoids (GCs) are among the most important drugs for acute lymphoblastic leukaemia (ALL), yet despite their clinical importance, the exact mechanisms involved in GC cytotoxicity and the development of resistance remain uncertain. We examined the baseline profile of a panel of T-ALL cell lines to determine factors that contribute to GC resistance without prior drug-selection.

Transcriptional profiling indicated GC-resistance in T-ALL was 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 conclude that in lymphocytes the activation of bioenergetic pathways required for proliferation may suppress the apoptotic potential and offset the metabolic crisis initiated 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.

The data also provided the first evidence that altered expression of wild-type ***MLL*** may contribute to GC-resistant phenotypes. Our findings warrant the continued development of selective metabolic inhibitors for the treatment of ALL.

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

Receptor mutation is not a common mechanism of naturally occurring glucocorticoid resistance in leukaemia cell lines

AH Beesley, RE Weller, S Senanayake, M Welch and UR Kees.

Glucocorticoids (GCs) are vital drugs for the treatment of acute lymphoblastic leukaemia (ALL). Cell lines cultured in high GC concentrations typically contain mutated glucocorticoid receptor (GR), something that is rarely found in primary ALL specimens.

We studied naturally occurring mechanisms of GC resistance and examined sensitivity to GC in 15 T-ALL cell lines grown without prior exposure to drugs. Resistance could not be attributed to mutations in GR or variations in levels of its expression. We conclude that this panel of cell lines provides a suitable ***in vitro*** model since it reflects GC resistance in primary ALL.

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

A preclinical model of relapse in acute lymphoblastic leukaemia

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

Despite significant improvements in the treatment of childhood T-ALL, as many as 30% of patients will relapse and most of those face a dismal prognosis. Understanding the genetic mechanisms underlying the development of drug resistance in T-ALL is critical and is likely to provide novel drug targets for exploitation. The goal of this study is to utilise a mouse xenograft model to answer fundamental questions regarding evolution of the drug-resistant cells, and the molecular pathways deregulated in the development of drug resistance ***in vivo***.

To represent a clinically relevant xenograft model of paediatric ALL, a 4-drug treatment regimen designed to mimic paediatric remission induction therapy has been developed in NOD/SCID mice. In contrast to the previously established 3-drug regimen containing vincristine, dexamethasone and L-asparaginase (designated VXL), we have developed a new experimental system combining VXL with an anthracycline daunorubicin (DNR). Our data indicated that DNR synergises with VXL to significantly delay disease progression, suggesting that a 4-drug model is of greater clinical relevance.

A microarray investigation was conducted to assess if spleen or bone marrow is the optimal tissue for analysis. Bone marrow is more commonly isolated from patients, however spleen tissue contains considerably higher blast cell numbers. Comparison of transcriptional profiles revealed an excellent correlation (0.9926) between cells harvested from the spleen and bone marrow. Therefore, cells isolated from spleens will be utilised for all subsequent microarray and clonality experiments.

Since cells harvested from spleens of NOD/SCID mice contain >95% human CD45+ cells and <5% mouse cells, we developed an experimental and bioinformatics approach to determine the effect of residual mouse RNA hybridisation to human Affymetrix GeneChip 1.0 ST Arrays. While hybridisation of mouse RNA does occur, mixing experiments demonstrated that <5% contamination does not significantly affect the sensitivity or specificity of the arrays.

To obtain species-specific transcriptional profiles an ***in silico*** bioinformatics approach to mask cross-hybridising probes is currently being investigated.

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

The role of BSG in acute lymphoblastic leukaemia and relapse

AH Beesley, RE Weller and UR Kees.

BSG (also known as CD147) is a trasmembrane glycoprotein implicated in tumorigenesis that we recently reported to be transcriptionally unregulated at relapse in acute lymphoblastic leukaemia (ALL). Here we report that ALL patient specimens also express highly glycosylated forms of BSG protein, particularly at relapse. Glycosylation patterns were extremely variable in ALL cell lines and were associated with a low frequency of ***BSG*** missense mutation. Inhibition of BSG failed to affect the drug-resistant phenotype or invasive potential of the highly-glycosylated PER-485 cell line. We conclude that ***BSG*** is a marker of aggressive ALL but its functional role remains to be determined.

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

Carcinomas

Novel BRD4 translocation in undifferentiated carcinoma

K Thompson, AH Beesley, J Rampellini and UR Kees, in collaboration with A Murch, King Edward Memorial Hospital for Women, Perth, Western Australia; and A Charles and M Phillipps, Princess Margaret Hospital, Perth, Western Australia.

Two years ago a 16 year old female patient was diagnosed at Princess Margaret Hospital (PMH) with a poorly differentiated lung carcinoma which had the hallmarks of a rare but almost invariably fatal carcinoma arising in the midline organs of young people. These cancers are characterised by translocations between chromosome 15 and 19 and in most cases the breakpoint on chromosome 19 contains the BRD4 bromodomain gene and the NUT gene on chromosome 15, which was present in cell line PER-403 established from an 11 year old girl diagnosed at PMH several

years ago.

The 16 year old patient received combination chemotherapy at PMH and she initially responded well, however died 8 months after diagnosis. We generated cell line PER-624 from her cancer cells and we have determined that they contain several karyotypic abnormalities, including t(6;19), t(1;18;7) and add(3). The t(6;19) breakpoint was confirmed by FISH to contain BRD4.

These findings indicated that the BRD4 translocation is not the only feature of this very aggressive disease and that the gene was translocated to a locus other than NUT on chromosome 15. Using several approaches the current aim is to define the translocation partner genes in this carcinoma and to determine whether transcripts are generated.

This work was supported by 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, CM Bertram, L Genovesi, 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 types 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 panel of CNS-PNET cell lines, primary CNS-PNET specimens, and human NSCs 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.

This work was supported by the NHMRC, Australia.

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

CM Bertram, S Egli, S Wong, UR Kees and PB Dallas in collaboration with SM Hawes and G Peh, Monash Immunology and Stem Cell Laboratories, Monash University and M Dottori Neuroscience, University of Melbourne.

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 stem cell biologists Dr Susan Hawes at the Australian Stem Cell Centre at Monash University, and Dr Mirella Dottori at the University of Melbourne, 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

This work was supported by the NHMRC, Australia.

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. 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. Reconstitution of ***FOXO1A*** expression in ***FOXO1A*** null cell lines does not reduce proliferation or induce apoptosis either under normal growth conditions or in response to chemotherapeutic agents. Consistent with these data, ***FOXO1A*** knockdown in NSCs does not affect proliferation. These results suggest that the down regulation of ***FOXO1A*** generally observed in CNS-PNETs may be linked to deregulated self-renewal or differentiation pathways during brain tumour development. We are currently investigating these possibilities. A detailed understanding of the 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.

This work is supported by the NHMRC, Australia

The characterisation of deregulated microRNA expression in paediatric brain tumours

L Genovesi, S Wong, UR Kees and PB Dallas in collaboration with KM Giles, Laboratory for Cancer Medicine, Western Australian Institute for Medical Research.

MicroRNAs (miRNAs) are a large class of short non-coding RNAs that regulate growth and development in eukaryotic cells. It is now clear that deregulated miRNA expression plays an important role in the pathogenesis of many different types of cancer, including adult brain tumours. Recent data suggest that deregulated miRNA expression may also play a significant role in the pathogenesis of CNS-PNETs. We are addressing this issue in more detail by analyzing the expression levels of a panel of 20 pre-selected miRNAs that were identified using bioinformatic approaches.

So far, these data indicate that ***miR-21*** is generally up-regulated in CNS-PNETs, similar to the situation reported for adult brain tumours. Three miRNAs that are predicted to target ***FOXO1A*** were also over-expressed in CNS-PNETs compared to NSCs raising the possibility that down-regulation of ***FOXO1A*** expression in CNS-PNETs may be linked to deregulated miRNA expression. To expand the miRNA study we plan to screen our panel of primary CNS-PNETs and NSCs for the expression of ~600 miRNAs. These data will then be correlated with the mRNA expression profiles from the same specimens.

We anticipate that the integration of mRNA and miRNA expression data has the potential to rationalise our understanding of the fundamental molecular mechanisms that initiate and maintain the brain tumour phenotype.

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

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Research Support

Stewart Cattach

Administrative Support

Joanne Graham

Theses passed

Nicholas Gottardo, MB ChB FRACP (Paeds.) PhD "Oncogenes and prognosis in paediatric T-cell acute lymphoblastic leukaemia" (co-supervisor Dr. D. L. Baker). University of Western Australia.

External Committees

International

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

National

Peter Dallas. Australian Society for Stem Cell Research, Steering Committee, (2008-)

Peter Dallas. Australian Neuroscience Initiative - Healthy Brains for our Children Working Party.

Regional

Ursula Kees. Cancer Council of Western Australia

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

Invited Presentations

Ursula Kees. ANZCHOG, Perth, Australia, May 2008. "Modeling therapy failure in paediatric acute lymphoblastic leukaemia".

Peter Dallas. ANZCHOG, Perth WA, May 2008. "A human neural stem cell model for the study of the pathogenesis of paediatric brain tumours".

Nicholas Gottardo. International Symposium Pediatric Neuro-Oncology (ISPNO), Chicago, USA June 2008. "Concurrent activation of Notch cell signaling and deletion of ***Ink4a/Arf*** in radial glia causes cerebral ependymoma". Received the ISPNO Young Investigator award for scientific excellence.

Ursula Kees. HSANZ, Perth, Australia, July 2008. "Insight into therapy failure in paediatric acute lymphoblastic leukaemia".

Ursula Kees. 5th International Workshop on the CCN Family of Genes, Toronto, Canada, October 2008. "The role of CTGF in paediatric acute lymphoblastic leukaemia".

Details of research Funding Awarded in 2008

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

Raine Priming Grant (2008 – 2009) awarded to Dr Peter Dallas, "The characterisation of deregulated microRNA expression in paediatric brain tumours".

Division of Clinical Sciences

The Divisional activities centre broadly around three main themes:

A) Asthma

Studies on the mechanisms underlying the development of asthma, involve longitudinal birth cohorts 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), and John Upham (University of Queensland), together with Deb Strickland (Cell Biology) and Phil Stumbles (Cell Biology and Murdoch University).

Significant achievements from the program grant during 2008 include:

1. Defining the antibody response in children with asthma exacerbations and the changes occurring during convalescence. *IgE to house dust mite allergens decreased while IgE to P6 antigen of the nasopharyngeal colonising bacterium* ***H. influenzae*** *increased to high titre. The already low IgG antibody levels of children admitted for asthma exacerbations did not recover and even fell during convalescence. The importance of the low IgG in the development was further elaborated by showing that children with frequent episodic or persistent asthma had lower titres than children with infrequent episodes.*

2. Defining a novel pathway responsible for amplifying innate immune responses to respiratory viral infections in atopics presenting with acute severe asthma. *Our data show, for the first time the role of pre-existing IgE antibodies in recruiting and amplifying the innate immune responses involving the pro-inflammatory alternatively activated macrophages during acute exacerbations of asthma in children.*

3. Identifying mechanisms by which airway epithelial cells regulate DC function. *Our data show that cytokines secreted by epithelial cells regulate maturation of airway mucosal dendritic cell maturation and function, in particular balancing the response to pathogenic and non-pathogenic stimuli.*

4. 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

(henceforth known as OMIP) to prevent the development of allergic sensitisation in asthma. This project represents a major collaborative venture between Peter Sly and Pat Holt (Cell Biology), together with A/ Professor Philip Robinson (Royal Children's Hospital, Melbourne) and Professor Hugh Sampson (Mt. Sinai Hospital, New York, USA). Over 15,000 doses of allergen or placebo have been given to 50 children without and treatment-related serious adverse events, demonstrating that immunoprophylaxis in high risk children is safe. This cohort has finished treatment and is now in the follow-up phase.

B) Early Detection of Lung Disease in Cystic Fibrosis

During 2008 we formalised the collaboration between Clinical Sciences; the Department of Respiratory Medicine, PMH; the Department of Respiratory Medicine, Royal Children's Hospital, Melbourne; and the Murdoch Children's Research Institute into the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF). We officially launched AREST CF and unveiled our website (www.arestcf.org) at a public function held at the Institute in December 2008. The community support bodies, Cystic Fibrosis Western Australia and Cystic Fibrosis Victoria partner with us in this venture. The program is extremely well accepted in both clinics with >95% of eligible families participating.

The **AREST CF program** *has grown from an early surveillance program initiated in Perth in 1999 that involved bronchoalveolar lavage (BAL) to evaluate pulmonary infection and inflammation and infant lung function testing. The program was extended to include measurement of preschool lung function in 2003 and chest computed tomography (CT) scanning in 2005. The Melbourne clinic joined the program in 2005 and we have been successfully operating as a single entity since. The current program consists of a comprehensive assessment soon after diagnosis (average age 3 months) and an annual assessment until age 6 years or when the child can expectorate sputum. Each assessment includes chest CT and BAL under general anaesthesia; lung function testing (infant techniques until age 2y, and pre-school techniques thereafter); assessment of pulmonary inflammation and infection from BAL; and research into novel markers of inflammation, oxidative stress and lung destruction in BAL and urine.*

Major findings and achievements of the current program:

1. Pulmonary inflammation is common in early life and increased in the presence of infection.

2. Decreased CFTR function, as indicated by sweat chloride levels, is associated with increased pulmonary inflammation.

3. Early pulmonary inflammation in CF is characterised by large numbers of neutrophils, increased levels of IL-8 and free myeloperoxidase and neutrophil elastase activity; 77% have detectable IL-8 and 30% have free neutrophil elastase in 3 month BAL. Free neutrophil elastase activity in BAL is a major risk factor for subsequent bronchiectasis.

4. 80% of children have at least 1 pulmonary infection by 6 years of age; 50% are asymptomatic at the time and 36% are infected with ***Pseudomonas aeruginosa*** *(early acquisition is a major risk factor for bronchiectasis).*

5. The median age of acquisition of ***Pseudomonas aeruginosa*** *is 26 months in children diagnosed following newborn screening.*

6. Pseudomonas aeruginosa *can be eradicated with aggressive treatment, with 77% of infections eradicated after a single treatment cycle of intravenous followed by oral and inhaled antibiotics.*

7. Lung function in preschoolers is worse in those with respiratory symptoms and pulmonary infection and can be used clinically in the same way as lung function in older children.

8. CT abnormalities are common in early life; with 18% having bronchial dilatation (bronchiectasis), 45% having bronchial wall thickening and 67% having gas-trapping at three months of age. These changes persist and are progressive in >70% of children on scans assessed 12 months apart. Forty percent of children have bronchiectasis by age 4 years.

On a sad note, Dr. Siobhain Brennan, who played a major role in establishing the program left us during 2008 to follow her dream and enrolled in the Postgraduate Medical course at UWA. We wish her all the best in her new career.

C) Children's Environmental Health

The Division of Clinical Sciences was designated as the WHO Collaborating Centre for Children's Environmental Health in July 2006. The terms of reference for the Centre are:

1. To conduct high quality research aimed at understanding the mechanisms underlying the development of diseases of environmental origin in children, with special emphasis on respiratory disease (e.g. respiratory infections, asthma & allergies).

2. To build research capacity by fostering collaborations between developed and developing nations.

3. To enhance the research capacity of researchers and health care professionals by providing access to high quality education and training.

4. To develop programs and curriculum to increase awareness about environmental threats, with special emphasis on respiratory diseases in children.

5. To develop methods for translating research findings into public policy and intervention strategies.

Further details about the Centre can be found on our website (www.ichr.uwa.edu.au/who)

The Centre is affiliated with the School of Public Health, Division of Health Sciences at Curtin University. The Centre Staff consist of coordinators for Environmental Science (Dr. Peter Franklin), Longitudinal studies (Dr. Merci Kusel), Education and Training (Dr. Leith Sly) and Public Policy (Professor Steven Zubrick) as well as administrative support and research staff. In 2008 Ms Tania Gavidia joined the staff. She undertook an internship at WHO headquarters in Geneva with Dr. Jenny Pronzcuk in Public Health and Environment.

Key activities of the Centre include research on the mechanisms underlying the development of environmentally-related diseases in children, mechanistic studies in laboratory animals; collaboration with researchers in developing countries including Argentina, Brasil, China, India, Mexico, Nepal and Thailand, and offering an online Graduate Certificate in Children's Environmental Health through Curtin University and Open Universities Australia. This course is also being translated into Spanish to be offered as part of the Masters program of the Instituto Nacional de Salud Publica, Cuernavaca, Mexico. The Graduate Certificate in Children's Environmental Health is also offered through Open Universities Australia.

During 2008 we accepted a commission from the Western Australian Department of Health to conduct an independent study of respiratory health

*and the association with air quality in Kwinana. This study, known as the **Kwinana Children's Respiratory Health Study** proposes to take a detailed quantitative approach to investigating the lung function of children in this area. Children from the local primary schools have been invited to participate in the study. Participation involves taking measurements of lung function in children whilst simultaneously monitoring the air quality in this area. By measuring the lung health of children, the air quality and other factors related to respiratory health in the area, and comparing the results to similar studies around Australia, variations in lung function, air quality and other risk factors related to respiratory health can be identified. More information can be found on the study website: www.ichr.uwa.edu.au/kwinana . The study is guided by a steering a steering group with representatives from the community, industry and local and state government.*

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.

Research Area: Respiratory Physiology

Ventilator-induced lung injury in infants

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 otherwise healthy lungs in a process known as ventilator induced lung injury (VILI). This process may be exacerbated further by the presence of the lung injury which required the need for mechanical ventilation in the first instance. The majority of research on VILI has been directed at adults in order to develop guidelines that are then extrapolated to children, however, it is well recognized that the susceptibility to VILI in infants and young children differs substantially from that of adults due to age related differences in physiology and chest wall compliance.

This project was initiated in 2006 with the aim, initially, to develop rodent models of VILI in mice of various ages with and without background lung injuries or complications. Initial studies found that infant (2 week old) mice were less susceptible to the induction of VILI in response to mechanical ventilation. As an extension of these studies we began comparing the susceptibility to VILI in 3 strains of mouse (BALB/c, C57BL/6, 129Sv) in order to investigate if there is an underlying genetic susceptibility to VILI. We found that strain has a considerable impact on the response to mechanical ventilation.

Recruitment manoeuvres (RMs) are used routinely in intensive care to recruit closed lung units, thus opening the lung and improving oxygenation. We found that "aggressive" and repeated recruitment manoeuvres did not cause excessive lung inflammation / injury in mice. In 2008, the models that were developed were applied to an adult model of influenza infection. These studies are ongoing and are designed to test the "two-hit" hypothesis whereby mechanical ventilation exacerbates the injury that resulted in the requirement for assisted ventilation.

In addition to these studies on mice, research using infant rat models of VILI was begun in 2008. The primary focus of these infant rat studies was to further examine the "two-hit" hypothesis by comparing different types of lung injury that commonly result in the requirement for mechanical ventilation in infants; acid aspiration, sepsis (systemic bacterial inflammation), pneumonia and haemorrhage. Preliminary studies were required to establish the right "dose" required to induce an appropriate level of injury in these models. We began testing the effect of different ventilation strategies and recruitment

manoeuvres in these injury models. Our primary conclusion from these studies so far is that, in contrast to adults, high tidal volume ventilation and aggressive recruitment manoeuvres improve lung compliance and oxygenation but do not induce significant additional lung injury in infant rats. These studies are continuing.

The influence of VEGF-D on lung development in health and disease.

Debra Turner, Graeme Zosky, Peter Sly,

External Collaborators: Teruhiko Sato and Marc Achen, Ludwig Institute for Cancer Research, Victoria

The vascular endothelial growth factor (VEGF) molecules (VEGF-A, B, C, D, placental growth factor) are 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 are 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 lung disease. 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. In 2007 we commenced this project with 21 wild-type controls and 23 VEGF-D knockout mice supplied 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 began a series of experiments to examine the role of VEGF-D in lung responses to disease. We compared baseline lung function in VEGF-D knockout and wild-type littermates 24 hours after intranasal inoculation with the bacterial product lipopolysaccharide (LPS) in saline or saline alone (control). While LPS induced significant lung inflammation as expected, VEGF-D knockout mice did not have higher levels of inflammation or impaired lung function in response to LPS compared to wild-type controls. Since VEGF-D did not appear to alter lung function in healthy or diseased lungs these studies were concluded at the end of 2008.

Murine models of allergic airways inflammation.

Graeme Zosky, Alexander Larcombe, Elizabeth Bozanich, Jennifer Burchell, Debra Turner and Peter Sly

In collaboration with Patrick Holt, Deborah Strickland, Matthew Wikstrom (Division of Cell Biology).

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 is designed to compliment our clinical studies and identify the mechanisms underlying lung dysfunction in asthma.

This project, which has been ongoing for a number of years, has assessed lung mechanics in response to allergen challenge. We have demonstrated that BALB/c mice systemically sensitised with ovalbumin (OVA) displayed limited early and no late phase lung function responses to OVA challenge. Complimentary studies examining the strain dependence of airway hyperresponsiveness (AHR) showed that BALB/c mice had increased responsiveness to the bronchocontrictor methacholine (MCh) following OVA challenge. This disparity between AHR and acute lung responses to allergen challenge highlights the limitations of mouse models of allergic airway responses.

In 2008 we followed up these studies in order to further elucidate the mechanisms of AHR. Firstly, we compared AHR responses in three strains of mouse; BALB/c, C57BL/6, 129Sv. We found that AHR is genetically determined with the BALB/c being the only strain to show airway specific responses. Using immunological data obtained from these strains, in conjunction with adoptive transfer experiments using DO11.10 T cell transgenic mice, we were able to link AHR to activated T cells in the airways.

In 2008 Jennifer Burchell completed her PhD studies which were aimed at determining the role of dendritic cells (DCs) and regulatory T cells (Tregs) in modulating AHR. These studies demonstrated that a single challenge with OVA in BALB/c mice systemically sensitised to OVA resulted in rapid uptake of antigen by DCs, the production of cytokines and development of AHR. In contrast, repeated OVA challenge resulted in tolerance and suppression of AHR. We have been able to show

that suppression of AHR is linked to the elevation of the number of Tregs in the airways. Likewise, transfer of Tregs into mice prior to a single OVA challenge resulted in suppression of AHR. This work is ongoing and is complimented by our collaborations with Cell Biology which involve studies examining the strain dependence of AHR in rat models of allergic airway disease and transgenic mice in order further elucidate the mechanisms of allergen induced AHR.

Arsenic induced non-malignant lung disease

Graeme Zosky, Peter Sly

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

Arsenic is a well recognised carcinogen and is listed by the International Agency for Research on Cancer (IARC) as a category 1 carcinogen. However, recent evidence from an exposure event in Chile has suggested that arsenic is linked to the development of non-malignant obstructive lung disease. In particular, ***in utero*** exposure to arsenic via drinking water has been linked to increased mortality due to bronchiectasis in young adults.

In order to investigate the link between early life arsenic exposure and the development of lung disease in later life we conducted a series of experiments using mouse models of ***in utero*** arsenic exposure. We began pilot studies in 2008 which involved exposing pregnant mice from three strains (C57BL/6, C3H/HeARC, BALB/c) to 100 ppb (or 0 ppb as a control) via their drinking water from gestational day 8 (prior to the development of the lung buds at day 9.5) until birth. The offspring of these mice had their lung function measured at 2 weeks of age. We found that there was no difference in lung mechanics corrected for lung volume in BALB/c mice exposed to arsenic compared to controls. In contrast C3H/HeARC mice exposed to arsenic had significantly higher airway resistance for a given lung volume compared to controls and arsenic exposed C57BL/6 had higher tissue damping and elastance for a given lung volume compared to controls. These experiments provided the proof of concept data required to demonstrate the potential of arsenic to alter lung development which may explain the link between early life arsenic exposure and poor lung health in later life. These studies are ongoing and we now plan to; i) construct full lung growth trajectories for arsenic exposed mice and controls, ii) determine if arsenic increases the severity of response to viral infection and, iii) identify arsenic sensitive pathways using microarray technology.

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

Alexander Larcombe, Elizabeth Bozanich, Peter Sly, Debra Turner.

External Collaborators: Rosa Gualano and Gary Anderson from the University of Melbourne

This study investigates 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). Early life respiratory viral infections alter lung function, increase airway responsiveness in humans and 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.

In the last few years we have established successful mouse models of RSV and flu using adult BALB/c mice. We were able to demonstrate that exposure to either virus, as an adult, results in acute AHR to methacholine (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 were able to confirm successful acute phase (~4 days after inoculation) viral infection and replication in addition to complete recovery in adult mice 3 weeks post inoculation. Data generated from this project formed the basis of a successful three year NHMRC grant (#458561 2007-2009).

We measured lung function, responses to methacholine (AHR) and inflammation in adult male and female BALB/c mice infected with influenza when adult. In these mice we found significant inflammation and AHR 4 days after infection which was cleared 21 days after infection. Of note were significant differences in the severity of AHR and inflammation between male and female mice. In almost all parameters studied, female mice displayed a more severe

disease state than male mice.

These studies were repeated using weanling (3 week old) mice to assess how a second host defense factor (age) influences response to respiratory viral infection. 3 week old mice also had significant AHR and cellular inflammation during the acute phase or infection, and female mice again were "sicker" than male mice. Whereas adult mice had completely recovered 21 days post infection, some measures of lung function (particular those associated with the lung parenchyma) did not return to baseline levels in 3 week old mice 21 days post infection.

These results suggest that age of infection has important impacts on the effect of respiratory viral infection. It is known that lung growth develops along trajectories, such that lung function at birth, or early in life largely predicts lung function later in life. Mice at 3 weeks of age are still growing, and it is likely that a severe respiratory viral infection at this age results in a downward shift in their normal growth trajectory, such that lung function in later life is negatively affected. Also in 2008 we began immunological analysis of dendritic and other antigen presenting cells harvested from mice exposed to influenza and/or antigen in early life. These data are still being analysed.

In 2008 we also began preliminary studies using a second common respiratory virus (rhinovirus – RV). We plan to repeat the above studies using this virus (rather than RSV) to examine the responses of mice to different viruses and hence determine whether AHR is viral-specific.

The effects of *in utero* tobacco smoke exposure in a murine model of asthma.

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

Unborn children exposed to tobacco smoke are more likely to suffer respiratory disorders such as bronchitis and wheeze after birth and are more likely to be admitted to hospital for respiratory problems. Exposure to cigarette smoke before and directly after birth affect a child's lung function, however, a mother's smoking during pregnancy, rather than her smoking status after the birth is more highly correlated with the development of childhood asthma and wheeze. There is an association between ***in utero*** exposure to cigarette smoke to reduced lung function and childhood asthma, however the mechanisms for this are unknown. We are in a unique position of being able to measure lung function in mice as young as two weeks old. By measuring lung function at 2, 4, 6 and 8 weeks of age we will be able to determine if ***in utero*** cigarette smoke exposure causes changes in lung growth that result in long term changes to lung function as an adult.

This project began in 2008. We began by characterizing our commercially available cigarette smoking machine. Adult female mice were exposed to different cigarette regimes for 13 days (the length of time pregnant mice would be exposed). At the end of this period BAL was collected for analysis of the resulting inflammatory cells. These studies led to an optimal regime of 3 cigarettes twice per day for 13 days. Mice exposed to this regime had an increase in total cells per mL in BAL of ~5 times above naïve levels which is similar to that seen in humans. Approximately one third of these cells were neutrophils. These mice exhibited no reduction in weight and appeared healthy throughout the study.

Following characterization of the smoking machine, we began experimentation with an initial group of twelve pregnant BALB/c dams. Half of these mice were exposed to six cigarettes per day for twelve days (the "smoke" group), and half were exposed to air for the same period of time (the "air" or control group). When the resultant pups were two weeks old, we measured their lung volumes, baseline lung function and lung mechanics over 20cm H_2O inflation/deflation manoeuvres. We are the only laboratory in the world that is able to make these measurements on two week old mice. Samples of lung tissue were taken for later analyses.

We identified significant differences in baseline lung volume between the two groups of pups with mice born from smoking mothers having significantly lower lung volumes compared to those born from non smoking mothers, despite being similar in mass. 2-week-old mice subjected to cigarette smoke ***in utero*** also had different volume dependencies of airway resistance, tissue damping, tissue elastance and hysteresivity compared to control mice. These data are the first to show impaired lung function in mice exposed to tobacco smoke ***in utero*** using appropriate techniques.

In 2009 we plan to study the same parameters outlined above in 4, 6 and 8 week old mice born from dams exposed to cigarette smoke or air during pregnancy, and potentially a repeat of these groups with mice subjected to our perinatal priming protocol. This protocol provides an ideal platform to test for the presence of synergistic interactions between ***in utero*** tobacco smoke exposure and early life allergic sensitisation.

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

Elizabeth Bozanich, Alexander Larcombe, Peter Sly, Debra Turner. External Collaborators: Rosa Gualano and

Gary Anderson from the University 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 sensitisation ***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 or vehicle exhaust emissions. The timing of the "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 hyper-responsiveness. The aim of this project is therefore to examine interactions between allergen sensitisation 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 sensitisation and ***viral infections*** in early life alter lung growth, airway function and AHR. In contrast, we propose the combination of allergic sensitisation and exposure to ***non-viral irritants***, such as air pollutants, can not provide the 'second hit" required to induce persistent asthma.

In earlier studies we developed a novel model of perinatal allergic priming which forms the basis of this project. BALB/c mice are primed with intranasal ovalbumin (OVA) on the day of birth and boosted with intranasal OVA 4 weeks later. Subsequent exposure to aerosolized OVA as an adult results in AHR. In addition we developed a model of early life infection by inoculating mice with influenza A at 1 week of age

In 2007 we began studies in neonatal mice inoculated with Influenza A at 1 week of age. We subsequently conducted some preliminary physiology experiments in this age group which allowed the development of our mouse model of early life respiratory virus infection. Previously all respiratory viral studies in our lab had used much older mice.

In 2008 we completed work on the neonatal mouse model of Influenza A infection and were able to demonstrate that, unlike mice infected as adults, neonatal mice exposed to virus at one week of age developed persistent AHR beyond clearance of the virus and subsequent resolution of inflammation. Also, it was evident that female mice in this age group had a greater degree of AHR than males. After the successful development of the perinatal allergen priming and neonatal viral exposure models, the project was then focused toward the interaction of Influenza A virus and antigen exposure early in life. This series of experiments was designed to test the specific hypothesis that ***"the combination of allergic sensitisation and viral LRI in early life interact synergistically to alter lung growth, airway function and AHR."*** Mice sensitized to OVA as newborns were infected with Influenza A (or media control) on day 7, and extensive physiological assessment of lung function, lung volume and pulmonary inflammation were performed at 2, 4, 6 and 8 weeks of age, along with assessments of AHR at 8 weeks.

Both neonatal exposure to Influenza A and antigen individually induced AHR in adult mice at 8 weeks of age, however, there was neither an additive or synergistic effect of the two exposures. These findings demonstrate that exposure to Influenza A virus or OVA during the neonatal period alter lung mechanics when challenged with MCh in adult mice. The measurement of baseline lung function and lung volume from 2-8 weeks of age will be used to construct growth trajectories to assess whether these early life interventions have long term effects on lung development.

Research Area: Cystic Fibrosis

Accuracy of serology at predicting *Pseudomonas aeruginosa* in young children with cystic fibrosis

Tonia Douglas, Siobhain Brennan, Luke Berry, Kaye Winfield, Stephen Stick, Peter Sly. External Collaborators: Claire Wainwright and Keith Grimwood from Royal Children's Hospital Brisbane, Queensland Children's Medical Research Institute

Pulmonary infection with ***Pseudomonas aeruginosa*** is an important event in the evolution of CF lung disease. Initial early infection in young children presents a window of opportunity where aggressive antibiotic treatment may eradicate ***Pseudomonas aeruginosa*** and potentially delay the establishment of chronic infection by mucoid strains with their associated adverse impact upon respiratory function and clinical status. Therefore there is strong incentive for accurate and early detection of ***Pseudomonas aeruginosa*** infection in young children.

Infection with ***Pseudomonas aeruginosa*** stimulates the production of antibodies to ***Pseudomonas aeruginosa*** 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.

The aim of this project was to determine whether serum antibodies raised against ***Pseudomonas aeruginosa*** antigens would aid the diagnosis of pulmonary infection with this organism in infants and young children.

Serum antibodies directed against ***Pseudomonas aeruginosa*** were measured using a semi-quantitative IgG-ELISA consisting of a multiple-antigenic blend (MAG) of 64 different ***Pseudomonas*** antigens from 17 of the most common serotypes. Levels of MAG were measured in a 'discovery' population and a 'test' population. Sera were collected at the time of BAL in children with CF.

Levels of MAG were detected in both the discover and test cohorts, however the levels did not accurately identify whether a child had a ***Pseudomonas aeruginosa*** infection in the lung. The sensitivity, specificity, positive predictive value and negative predictive value in the test population were 0.46, 0.82, 0.43 and 0.84, respectively for BAL culture. In the discovery population, levels of MAG were associated with number of neutrophils, neutrophil elastase and interleukin-8. These levels were not tested for in the discover cohort.

In conclusion, the positive predictive value of serology was too poor to usefully serve as a non-invasive marker of ***Pseudomonas aeruginosa*** acquisition for lower respiratory infection in young children with CF.

Oxidative stress induced lung injury in children with cystic fibrosis

Luke Garratt, Siobhain Brennan, Peter Sly. External Collaborators: Anthony Kettle, Department of Pathology, University of Otago, Christchurch, New Zealand; Marcus Cooke, University of Leicester, United Kingdom; Jonathon Grigg, Centre for Paediatrics, Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry

Lung disease begins in children as young as 6 weeks of age with intermittent infection and inflammation occurring in the pre-school years. Activation of innate host defence by the presence of microbes in the lungs results in the generation of reactive oxygen species (ROS). Oxidative stress occurs when the generation of ROS exceeds the capacity of the oxidant defences, resulting in tissue damage.

The first aim of this study was to validate the use of urinary 8-oxoDG as a sensitive and reliable biomarker of oxidative stress injury in the lungs of young children with CF. We have found that levels of 8-oxoDG in urine were associated with levels of 3-chlorotyrosine, a marker of oxidative stress, in the bronchoalveolar lavage fluid of children with CF. This demonstrates, urinary 8-oxoDG can be used as a biomarker of oxidative stress lung injury.

Secondly we wanted to compare levels of urinary 8-oxoDG in children with CF to healthy controls. Levels of 8-oxoDG in the urine decrease with age, therefore after adjusting for this, children with CF have higher levels of 8-oxoDG in their urine compared to non-CF controls.

The final aim of this project is to establish whether urinary 8-oxoDG can be used as an outcome variable for clinical trials of anti-oxidant therapies to prevent destructive lung disease in young children with CF. Currently this area of research is still in progress and will continue in 2009 where we will determine relationships between levels of 8-oxoDG and clinical respiratory factors such as inflammation, infection and structural lung damage.

Respiratory burst response of circulating granulocytes in children with cystic fibrosis

Luke Garratt, Siobhain Brennan, Peter Sly

Whether inflammation observed in CF arises in the absence of infection is still a matter of debate, though it is certain that episodes of infection do exacerbate inflammation. Ascertaining leukocyte function in early-life CF, particularly for neutrophils which eventuate as the predominant pulmonary leukocyte, in conjunction with other pulmonary assessments should provide further insights into progression of inflammation in CF. A critical part of neutrophil function is the ability to produce ROS that are used in a controlled manner for the destruction of ingested microbes and particle. Therefore, we investigated respiratory burst responses of circulating granulocytes in infants and pre-school children.

Whole blood leukocytes were stimulated by either opsonised ***E. coli*** or the chemical ligand PMA to assess functional response or the maximal response respectively. ROS production was quantified by the addition of a reporter substrate that fluoresces once oxidised. Assays were performed in duplicate and the mean result was reported. We also performed BAL for microbiology, cytology and inflammation assessments and high resolution CT's to radiologically assess lung damage. Two components of the neutrophil oxidative pathway were also measured in the lavage fluid, the neutrophilic enzyme myeloperoxidase which produces the neutrophil oxidant hypochlorous acid, and GSA, the irreversibly oxidised isomer of the anti-oxidant molecule glutathione.

Our first aim was to identify if

granulocytes in CF subjects (n = 44, 0.25 – 8 years) exhibited any altered function to controls (n = 18, 0.5 – 7 years) with regards to ROS production. We have found that for both cohorts the maximal response of granulocyte decreased with age (CF r = -0.36, $p<0.05$; controls r = -0.51, $p<0.05$), however the functional response did not relate to age for either cohort. We also observed that for the CF cohort, the mean response of granulocytes to maximal stimulation was significantly higher than those of similarly aged controls (614 vs 409, $p<0.01$). Their responses to stimulation with opsonised bacteria were also above that of controls (216 vs 185), though this difference was not significant. The resting rate of the groups was similar (60 vs 63).

In addition to these observations a degree of heterogeneity was apparent in the respiratory burst responses of subjects. This heterogeneity did not reveal any relationship with infection status, history of ***Pseudomonas aeruginosa*** infection or inflammatory markers in the lung.

For a subset of our CF cohort (n = 6) it was noted that they had a significantly subdued capability to increase ROS production over resting rate (cf controls: 236 vs 409). The deficient capability was explained by either a subdued maximal response or an elevated resting rate. This subset fell below the 95% confidence limits of our controls and subjects in this subset were more likely to exhibit worse outcomes of disease, including elevated pulmonary neutrophil count, increased levels of myeloperoxidase and GSA and an increased extent of bronchiectasis, than those subjects with normal or enhanced ROS production.

Research is still in progress as we aim to develop a larger cohort of control results and look at any longitudinal changes that occur with age and infection.

Salivary IgA antibodies to *Pseudomonas aeruginosa* as a marker of early infection in children with cystic fibrosis

Luke Garratt, Tonia Douglas, Siobhain Brennan, Stephen Stick, Peter Sly.
External collaborators: Peter Richmond, School of Paediatrics and Child Health, Princess Margaret Hospital, Perth

Pseudomonas aeruginosa is a significant opportunistic lung pathogen in individuals with cystic fibrosis (CF) and is associated with increased lung disease and morbidity. Early intervention is beneficial for the effective clearance of ***Pseudomonas aeruginosa*** and better long-term health outcomes. Currently, lung flora of CF patients is monitored by regular culturing of sputum, however, children unable to expectorate are limited to annual BAL, which is invasive and requires general anaesthesia. Saliva is useful for clinical assays as collection is simple and non-invasive. We are developing a standardised enzyme-linked immunosorbent assay (ELISA) to detect a serological response to respiratory infection of ***Pseudomonas aeruginosa*** in children with CF who cannot expectorate.

18 children (7-18 years) with CF and recent ***Pseudomonas aeruginosa*** lung infection history and 16 non CF children (1-6 years) with no previous ***Pseudomonas aeruginosa*** infection history provided saliva as positive and negative controls, respectively. Saliva was obtained by spitting or absorbed using cellulose swabs and later extracted. These cell-free supernatant samples were used in an ELISA anti- ***Pseudomonas aeruginosa*** IgA using commercial antigen. All results were standardised to account for flow using total IgA expression.

Median value was increased 9 fold in the cent ***Pseudomonas aeruginosa*** lung infection group (Mann-Whitney test, $n=34$, $p\leq0.001$). There was no significant difference between mucoid and non-mucoid samples, and detection was independent of density (cfu/ml).

Early findings support that ***Pseudomonas aeruginosa*** respiratory infection can be detected through specific analysis of salivary IgA expression. Larger population sampling (30 positive, 90 negative) will aid selection of cut-off values for specificity and sensitivity testing in the future to objectively determine the utility of this assay as a means of monitoring for ***Pseudomonas aeruginosa*** and for determining effectiveness of treatment.

Acquisition and eradication of *Pseudomonas aeruginosa* in young children with cystic fibrosis

Tonia Douglas, Siobhain Brennan, Samantha Gard, Luke Berry, Catherine Gangell, Stephen Stick, Peter Sly

Lung disease in cystic fibrosis begins early in life and infections with***Pseudomonas aeruginosa*** are associated with worse prognosis. The aim of this study was to determine the population prevalence and age of acquisition of pulmonary infections with ***Pseudomonas aeruginosa***, and to report the effect of the current eradication therapy in our population.

Children under the age of six years with cystic fibrosis who participate in the Early Surveillance Program through AREST CF were included in the study. These children undergo an annual BAL for microbiological surveillance. When ***Pseudomonas aeruginosa*** was detected at BAL an eradication program using combined treatment with intravenous, oral and nebulised antibiotics was undertaken. A repeat BAL was performed 3 months following treatment to assess

eradication success.

Pseudomonas aeruginosa was detected in 28% of children with a median (range) age of detection 30.5 (3.3–71.4) months and was not associated with the presence of respiratory symptoms. Children infected with ***Pseudomonas aeruginosa*** had increased inflammation compared to children infected with organisms other than ***Pseudomonas aeruginosa***. Following eradication therapy ***Pseudomonas aeruginosa*** was eradicated in 77% of children following one eradication cycle, and in a total of 88% of children following a second cycle. The median (range) duration of eradication was 19 (3-69) months and was limited by the duration of follow-up available. Eradication was associated with a decrease in levels of inflammatory markers.

Pseudomonas aeruginosa was detectable in 28% of the population, with infections in children as young as 3 months. Infections with ***Pseudomonas aeruginosa*** were not associated with respiratory symptoms highlighting the importance of routine surveillance in addition to respiratory cultures at pulmonary exacerbation. Eradication of ***Pseudomonas aeruginosa*** is achievable in young children with cystic fibrosis to up to a period of five years using a combination of intravenous, oral and nebulised antibiotic therapy. Eradication of ***Pseudomonas aeruginosa*** is associated with reduced pulmonary inflammation.

Collaborative studies

Australian Clonal Pseudomonas in Cystic Fibrosis Study

AREST CF and Dr Tim Kidd and Professor Scott Bell.

Research Area: 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. External Collaborators: Richard Loh from the Department of Clinical Immunology, Princess Margaret Hospital, Perth

This cohort of 263 children at high genetic risk of atopy was recruited between 1996-1998. The children were followed closely for the first 5 years and extensive data on early respiratory infections, development of allergic diseases such as eczema and asthma, as well as wheeze was collected. We demonstrated significant associations between rhinovirus and RSV-induced wheezy LRI in the first year of life and the subsequent development of persistent wheeze at 5 years.

The 10 year follow-up visit commenced in July 2006 and was completed in August 2008. Data on the children's health as well as environmental exposures since the last follow-up visit at 5 years was collected. The children underwent blood tests, skin prick tests for atopy and lung function tests. Data from this follow up visit will help us to determine early life factors associated with persistent wheezing and asthma. It will also enhance our understanding of innate and adaptive immune system development as well as factors involved in the development and maturation of the immune system.

We acknowledge the ongoing commitment and support of the study children and their families.

Research Area: Clinical Respiratory Physiology

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

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 CF We are monitoring lung function in all infants diagnosed with CF 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, 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 FE_{NO} 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 studies 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 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:

1. Room temperature significantly influences all aspects of the exhaled breath temperature profile

2. Vital capacity strongly influence exhaled breath temperature in healthy children

3. After accounting for room temperature and lung volume, atopy, hayfever and airway hyper-responsiveness had no statistically significant influence on exhaled breath temperature.

Staff and Students

Head of Division

Peter D Sly MD MBBS DSc FRACP

Research Staff

Siobhain Brennan PhD

Vincenzo Cannizzaro MD

Tonia Douglas MBChB MRCPCH

Smilja Drogovich BPsych

Carlie Dunford BSc

K.E (Bill) Finucane (Emeritus Professor)

Felicity S Flack PhD

Rachel Foong

Peter Franklin

Catherine Gangell PhD (Adjunct Lecturer, Centre for Child Health Research UWA)

Luke Garratt

Tania Gavidia

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

Merci Kusel MBBS PhD, Grad Cert Nutritional & Environmental Health

Alexander Larcombe PhD (Adjunct Lecturer, Centre for Child Health Research UWA)

Faith Parsons

Leith Sly

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

Britta von Ungern Sternberg

Graeme Zosky PhD (Adjunct Lecturer, Centre for Child Health Research UWA)

Postgraduate Students

Angela Alessandri MBBS FRACP (Paeds), MBioeth PhD Candidate

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

Lisha van Reyk BSc(Hons) PhD Candidate

Liz Bozanich PhD Candidate

Lauren Mott MBBS PhD Candidate

Jennifer Burchell BSc(Hons) PhD Candidate

Research Support

Luke Berry – Laboratory Manager

Cameron Brooke

Claire Fowler

Jessica Lynch BSc

Theses passed

Lisha van Reyk, PhD "HPA axis responsiveness in adolescence and its

relationship with anxiety, asthma and atopy". University of Western Australia

Catherine Louise Gangell, PhD "Evaluation of the Forced Oscillation Technique for Clinical Assessment of Young Children with Cystic Fibrosis". University of Western Australia

Jennifer Theresa Burchell, PhD "The role of regulatory T cells and dendritic cells in allergen-induced airways hyperresponsiveness". University of Western Australia

David N. Baldwin, PhD "Impact of maturation and disease in respiratory system dynamics in infants". University of Western Australia

Awards

Graeme Zosky Asia Pacific Society of Respirology Travel Award to attend American Thoracic Society AGM

Alexander Larcombe Thoracic Society of Australia and New Zealand (TSANZ) Travel Award 2008

Alexander Larcombe Asia Pacific Society of Respirology (APSR) Travel Award 2008

Elizabeth Bozanich Asthma Foundation of WA Top-up Scholarship (2008-2009)

Elizabeth Bozanich Perron Award for Meritorious Performance (2008)

Elizabeth Bozanich GSK Post-Graduate Support Grant (2008-2009)

External Committees

International

Peter Sly Pacific Basin Consortium on Environment and Health, Chairman of Board of Directors

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, Scientific Advisory Committee

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:

Peter Sly Collegium Ramazzini

National

Peter Sly Asthma Australian Medical and Scientific Advisory Committee

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

Regional

Peter Sly Intellectual Property Management Group, Department of Health WA (Chairman)

Peter Sly Telethon Institute for Child Health Research Executive Committee

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

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

Peter Sly Asthma Foundation of Western Australia Medical Advisory Committee

Debra Turner Board of Directors, Scitech, Western Australia

Graeme Zosky Thoracic Society of Australia and New Zealand (W.A. Branch) Executive Committee

Internal Committees

Elizabeth Bozanich ICHR Social Club Committee – Secretary

Carlie Dunford ICHR Social Club Committee

Claire Fowler Eco-House Committee (Secretary)

Catherine Gangell Consumer and Community Council

Alexander Larcombe IT Steering Committee

Graeme Zosky Animal Research Centre Management Committee (Chairman)

Graeme Zosky Data Management and Services Steering Committee

Graeme Zosky Postdoc Committee

Invited Presentations

Peter Sly Children's Environmental Health in Australia. 3rd Scientific Conference for Environment and Health in Southeast and East Asia. Jeju Island, Korea, April 2008.

Peter Sly Effects of Pollution: Antenatal and Postnatal, Indoor and Outdoor. European Respiratory Society Annual Congress, Berlin, October 2008.

Peter Sly Impact of Environmental

Tobacco Smoke on Respiratory and Immune System Development. 41st Annual Meeting of the Chilean Society of Respiratory Diseases, Chile, November 2008.

Peter Sly Mechanisms of Early Pulmonary Disease: Early Disease Surveillance. 31st European Cystic Fibrosis Conference, Prague, June 2008.

Peter Sly Effects of Air Pollution on Respiratory Health in Children. 41st Annual Meeting of the Chilean Society of Respiratory Diseases, Chile, November 2008.

Peter Sly Prevention of Allergic Asthma in Children. 41st Annual Meeting of the Chilean Society of Respiratory Diseases, Chile, November 2008.

Peter Sly Wheezing Disorders in Children. 13th Congress the Asian Pacific Society of Respirology (APSR), November 2008.

Peter Sly Impact of tobacco smoking on growth and development of children and asthma risk. Jakarta, April 2008.

Peter Sly Susceptibility and Allergenicity of Children to Hazardous Chemicals. Korean FDA, Seoul, April 2008.

Peter Sly Animal models of respiratory disease. AstraZeneca, Lund, Sweden. October 2008.

Peter Sly Vulnerability of Children to Air Pollution. Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Melbourne, 2008.

Peter Sly Clinical Outcomes in Early Life Children with CF. Cystic Fibrosis Australia, Perth, March 2008

Peter Sly Lung function testing in pre-school children: ready for clinics? Overview of role of tests in clinical practice. Thoracic Society of Australia and New Zealand, Annual Scientific Meeting March 2008.

Peter Sly Management of Pre-School Wheeze. Mechanisms, Aetiology and Novel Treatments. Thoracic Society of Australia and New Zealand, Annual Scientific Meeting March 2008.

Peter Sly Future Paediatric Research Directions in Asthma. Australian Asthma Conference, Sydney, October 2008.

Internal collaborations

Graeme Zosky:-

1. 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)

2. Characterisation of mouse respiratory tract antigen presenting cell and dendritic cell populations and their response during allergic airway inflammation and early life viral infection (Phil Stumbles, Division of Cell Biology)

Alexander Larcombe:-

3. 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)

4. Characterisation of mouse respiratory tract antigen presenting cell and dendritic cell populations and their response during allergic airway inflammation and early life viral infection (Phil Stumbles, Division of Cell Biology)

5. 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

Elizabeth Bozanich:-

The role of activated T-cells in the mouse airway (with Philip Stumbles, Matt Wikstrom and Patrick Holt, Division of Cell Biology)

External Collaborations:

Gary Anderson, Rosa Gualano, Department of Pharmacology, University of Melbourne

Anthony Kettle, Department of Pathology, University of Otago, Christchurch, New Zealand

Marcus Cooke, University of Leicester, United Kingdom

Jonathon Grigg, Centre for Paediatrics, Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry

Division of Genetics and Health

The primary aim of the new Division of Genetics and Health at TICHR 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, 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 Division build on the group's previous interests in genetic susceptibility to infectious diseases through research undertaken at the Cambridge Institute for Medical Research (CIMR), Cambridge, UK, as well as on new and collaborative projects being established for the first time at TICHR. Jenefer Blackwell, Head of the Division, retains a position as Honorary Senior Scientist and Affiliated Principal Investigator at CIMR, allowing her to maintain a small laboratory in Cambridge to underpin continuing studies based in the UK and overseas. The work described here covers interests across both laboratories.

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

Research Area - Genetics of Complex Disease

Genome-wide association study of visceral leishmaniasis

Jenefer M Blackwell, * Heather Cordell, Michaela Fakiola, Richard Francis, * Muntaser Ibrahim, * Selma Jeronimo, Sanjana Mehrotra, E. Nancy Miller, Anshuman Mishra, Joyce Oommen, Christopher Peacock, * Shyam Sundar, * Mary Wilson (* International CIs)

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

We have now accumulated sample sizes of sufficient power to carry out hypothesis-driven candidate gene allelic association studies with confidence, and to perform SNP-chip based genome-wide association scans (GWAS). As part of the Wellcome Trust Case Control Consortium (WTCCC2), we are undertaking a GWAS of 1000 unrelated cases and 1000 unrelated controls from India, as well as 626 VL cases in families in which 1260 offspring have DTH measured as a quantitative trait (total 2250 individuals with parents) from Brazil, and 169 cases in multi-case families from Sudan. In total, 4880 DNAs are being analysed using Illumina 660W QUAD beadchip that contain 558,000 SNPs and 82,000 probes to detect CNVs. The data will be available during 2009. Ongoing projects in the lab are designed to capitalize on the output of the GWAS to identify functional pathways in pathogenesis, knowledge of which can underpin the development of novel therapies and interventions.

Funders of the project. The Wellcome Trust and the NIH

Candidate gene and genome-wide association studies of otitis media

Sarra Jamieson, Jenefer M Blackwell, David Burgner, Harvey Coates, * Heather Cordell, Richard Francis, Joyce Oommen, Elizabeth Scaman, Wendy Sun, Shyan Vijayasekaran, Selma Wiertsema (* International CI)

Otitis media (OM) is a global health

issue. It is the most common reason for children to visit a physician in the first years of life, for antibiotic treatment, and for surgery in young children. Treatment is at great cost to health services, vaccines are thus far ineffective, and children susceptible to recurrent disease may have permanent hearing loss with associated developmental problems. Adoptee and twin studies in Caucasian populations show that susceptibility to rAOM is highly heritable.

To identify the genes that contribute to recurrent acute otitis media (rAOM), we established the **Family Study of Ear Infections in Western Australian (WA) Children** (http://www.ichr.uwa.edu.au/om). We are currently collecting salivary DNA from 1000 identified rAOM index cases plus parents or unaffected sibling(s) where parent(s) are missing. Inclusion criteria for rAOM are ≥3 episodes acute physician-diagnosed ear infection at age ≤3 years and grommets inserted or recommended. Questionnaire data provides qualitative and quantitative information on environmental risk factors or covariates. These samples are being used currently for candidate gene analysis, with funding proposals under consideration to carry out a GWAS in WA comparing rAOM cases with available control data from the WA Pregnancy (Raine) Cohort Study and the WTCCC. The results will be replicated in sample from USA, UK and The Netherlands through the recent establishment of an international OM Consortium. Through this initiative, we have coordinated availability of DNA from >2400 rAOM cases that, when compared to data from >10,000 common controls, will provide a powerful resource to identify the ***genes*** and ***gene x environment*** risk factors that influence susceptibility to rAOM. This will provide unique and novel insights into the pathogenesis of rAOM that can inform future intervention strategies.

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

Genetics and epigenetics of congenitally acquired diseases

Sarra Jamieson, Natasha Nassar, Jenefer M Blackwell, Goh Ee Hui

Research initiated in Cambridge looked at genetic and epigenetic effects in susceptibility to clinical signs acquired following congenital infection with the ubiquitous protozoan parasite causing toxoplasmosis. Further work to understand the molecular basis of the epigenetic effects, and whether the parasite itself can influence epigenetic regulation of mammalian host genes, is continuing at TICHR. This forms the basis to expanding research on congenital diseases that build on the strong history of analysis of birth defects at the Institute. A new collaboration in this area has been established with Natasha Nassar in the Division of Population Sciences to look for gene by environment interactions that determine rising rates of hypospadias in WA.

Funders of the project. British Guide Dogs for the Blind Association, Cancer Research Council, University of Western Australia

Family study of ear health and metabolic diseases in a WA Aboriginal community

Jenefer Blackwell, Sarra Jamieson, Harvey Coates, * Heather Cordell, Elizabeth Davis, Elizabeth Scaman, Shyan Vijayasekaran (* International CI)

Understanding health and disease in Aboriginal communities could play an important role in reducing the disparity between Aboriginal and non-Aboriginal populations in Australia. The results of the WA Aboriginal Child Health Survey (WAACHS) undertaken at TICHR demonstrated the great potential for Aboriginal Health Services (AHS) and research organizations to build sustained partnerships to work in key health areas. This will underpin research designed to develop a better understanding of how heritable and environmental risk factors interact to determine the pathogenesis of disease, and to use this knowledge to underpin the development of more effective intervention strategies in the future. To this end, a partnership has been established between the Nganggawili Aboriginal Health Service (NAHS) at Wiluna in WA and TICHR, underpinned by the signing of memoranda of understanding (MoU) between NAHS and TICHR, and between NAHS, Karalundi Aboriginal Educational Community Inc. (KAEC; which is serviced clinically by NAHS) and TICHR. These MoUs incorporate the principles for research in Aboriginal communities as outlined within the framework of the NHMRC and other national guidelines, as recommended by the WA Aboriginal Health and Information Ethics Committee (WAAHIEC).

The first study bound by these MoUs deals specifically with the development of a joint family-based program around ear health in children, and the antecedents to the high incidence of type 2 diabetes (T2D) and related diseases (e.g. heart disease, renal failure) in adults, in the Aboriginal community serviced by NAHS. These are areas of great concern to this local community. The specific scientific aim of the research is to carry out a family-based study that will provide genetic data that will be informative about heritable risk factors and the pathogenesis of disease, and has the potential to provide genetic

indicators of environmental risk factors for disease. The study will address the areas of ear health and metabolic diseases, but the genetic data obtained have potential application to analysis of all health problems in this community (e.g. infectious diseases, scabies, cancer, etc.). The underpinning philosophy is that novel research should be undertaken in conjunction with provision of better educational and control protocols based on current knowledge. The results of this study should be broadly applicable to similar clinical concerns of other WA Aboriginal communities, and could inform treatment and translational research strategies across Aboriginal and Torres Strait Islander communities.

Genetics at the interface between type 2 diabetes and infection in Thailand

Jenefer M Blackwell, *Gregory Bancroft, Richard Francis, Sarra Jamieson, *Sunee Korbrisate, *Ganjana Lertmemonkolchai, Christopher Peacock (* International CIs)

In this project, we have brought together a team of scientists from Thailand and Australia, supported by key collaborators from the UK, to tackle the important problem of sepsis caused by ***Burkholderia pseudomallei*** and other bacterial pathogens in Thailand, and the role that T2D plays as a risk factor for severe disease. The underlying strategy for this project is to use genetics to understand the interaction between T2D and sepsis, especially melioidosis, in Thailand. A major aim is to build a DNA resource that will eventually permit GWAS to uncover, in a non-hypothesis-driven approach, novel genes/mechanisms/risk factors that determine this interaction. In the process of developing this resource, there is an opportunity to examine candidate genes that have arisen (a) through GWAS being undertaken for T2D and for bacteremia in other countries; and (b) as strong hypothesis-driven candidates for their roles either as genes for sepsis ***per se***, or specifically for melioidosis, in relation to iron homeostasis in both pathogen and host. Some of these candidate genes may also explain the interaction with T2D.

Overall, the combination of results of host genetic, intermediate phenotype, functional, and pathogen-specific data will help to define immunological, biochemical, metabolic, and molecular pathways that are important in determining heritable and environmental risk, pathogenesis, and the interplay between T2D and sepsis.

Funders of the project. Commission for Higher Education, Thailand

Research Area – Parasite Genomics and Vaccine Studies

Comparative analysis of human and kangaroo leishmania: defining human pathogenicity genes

Christopher Peacock, Jenefer Blackwell, Richard Francis

Leishmaniasis is a major global disease that affects millions and kills many thousands of people. There are no vaccines, prophylaxis and the few drugs that are available are toxic and difficult to deliver. This project is using the non-human pathogenic strain of leishmania recently discovered in Australia as a model to identify and characterize genes that control leishmaniasis in humans. The major aims of the project are to: (i) sequence the ***Leishmania*** species that is non-pathogenic to humans and make a full genome comparison to three published species representing the full spectrum of human disease; (2) develop molecular biological transfection techniques to experimentally confirm, ***in vitro*** and ***in vivo***, the function of putative pathogenicity genes; and (3) use the transfected parasites to develop a potential attenuated vaccine using an appropriate mouse model of infection.

Funders of the project. Core (see above)

Collaborative development of a vaccine against cutaneous and visceral leishmaniasis

Jenefer Blackwell, * Diane McMahon-Pratt, E. Nancy Miller, * Mary Wilson (* International CIs)

Leishmania are protozoan parasites that cause severe and debilitating cutaneous, as well as fatal visceral, disease in sub-tropical/tropical regions of Old and New Worlds. There are no vaccines in routine use. Despite the need for vaccines, there are challenges facing ***Leishmania*** vaccine development: (1) to find a vaccine that will cross-protect against the different forms of disease [i.e., visceral, cutaneous, or mucosal leishmaniasis]; (2) to induce long-lasting immunity, and (3) to identify key immune responses in vaccine-induced protective immunity.

This project represents a collaborative effort between three laboratories working on the unified theme of vaccine development against leishmaniasis. In Cambridge, the Blackwell laboratory used DNA vaccination in mice to screen 100 unique ***Leishmania*** genes as vaccine candidates against high dose virulent ***L. major*** infection. Fourteen novel and reproducibly protective antigens were identified. Mary Wilson's lab at the University of Iowa discovered six novel antigens through cDNA library screening with immune serum and T cells.

At Yale University, Diane McMahon-Pratt's

lab had 4 well-characterized antigens which protected against ***L. amazonensis*** and/or ***L. infantum*** infection. This provided a total of 24 potentially protective novel antigens that can ultimately contribute to a vaccine to be taken forward into canine and/or human trials to reduce the incidence of human disease. To make the best selection of antigens for such a vaccine, this project is re-evaluating the protection provided by 20 of these antigens against both Old World and New World species, optimizing delivery systems, and determining the key immunological correlates of protection.

Funders of the project. NIH.

Immunogenicity and efficacy trials of a DNA/MVA vaccine against canine leishmaniasis

Jenefer Blackwell, * Maria Antoniou, * Orin Courtenay, * Diane McMahon-Pratt, Christopher Peacock, * Mary Wilson, (* International CIs)

Studies in the Cambridge lab have thus far identified prime/boost vaccination with DNA/Modified Vaccinia virus Ankara (MVA) using the leishmanial antigen tryparedoxin peroxidase (TRYP) as the most protective vaccine producing long term immunity in mice. The major aims of this study are: (1) to conduct safety (Phase I) and immunogenicity (Phase IIa) trials of a DNA/MVA TRYP ***Leishmania*** vaccine in kenneled dogs; and (2) to conduct a community-based Phase IIb/III field trial to reduce canine zoonotic visceral leishmaniasis infection, disease and infectiousness in a genetically diverse population of dogs exposed to natural infection with ***L. infantum*** on Crete. Phase III outcomes include clinical disease, parasite load as a marker of infectiousness to sand flies, and immunological correlates of these end points (***in vitro*** cytokine stimulation assays, serology, and tissue cytokine mRNA expression).

Analysis will show differences in the incidence of infection and clinical disease between fully blinded and randomized vaccine and control groups, and related to measured immunological responses. A successful canine vaccine will protect dogs against ***Leishmania*** infection and/or disease, and reduce or eliminate infectiousness of the reservoir host, thereby reducing or preventing transmission to humans.

Funders of the project: Pfizer Inc.

Staff and Students

Head of Division

Jenefer M. Blackwell BSc(Hons) PhD FMedSci DSc

Professor in Genetics and Health, University of Western Australia

Head, Division of Genetics and Health, Telethon Institute for Child Health Research, WA

Honorary Senior Scientist and Affiliated Principal Investigator, Cambridge Institute for Medical Research, Cambridge, UK

Research Staff

*Michaela Fakiola ***BSc(Hons), MSc, PhD***

Sarra Jamieson ***BSc(Hons)***, ***MSc*** (Med Genet), ***PhD***

*E. Nancy Miller ***BA(Hons), PhD***

Joyce Oommen ***BSc***, ***MSc*** (Biol Sci), ***Dip Bioinf***, ***MSc*** (Immunol),

Christopher Peacock ***BSc, FIMLS***, ***PhD***

(* Cambridge Lab)

Postgraduate Students

Sanjana Mehrotra ***BSc(Hons) PhD Candidate (India)***

*Anshuman Mishra ***BSc(Hons) PhD Candidate (India)***

Goh Ee Hui ***BSc Honours Candidate***

(* Cambridge Lab)

Research Support

Elizabeth Scaman ***BA(Hons)***

Wendy Sun ***BSc(Hons)***

Awards

Sarra Jamieson, Friends of the Institute Margaret River Branch Award, 2008.

Sarra Jamieson, Child Health Research Foundation of WA Research Fellowship, 2009-2011

External Committees

International

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

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

National

Jenefer Blackwell, Expert Adviser, NHMRC Program Grant Panel, May 2008

Jenefer Blackwell, Member of the NHMRC Fellowships Panel, May 2008

Local

Jenefer Blackwell, Organizing Committee, HGSA-GRaPH-Int International Congress 2009

Sarra Jamieson, Treasurer, Perth Epidemiology Group, 2008+

Invited Presentations

Jenefer Blackwell, Royal College of Pathologists of Australia "Pathology Update", 14-16 March, Sydney, Australia.

Jenefer Blackwell, Australian Society of Parasitology Annual Conference, Plenary speaker, 6-9 July, Glenelg, South Australia.

Jenefer Blackwell, Brazilian NIH Tropical Medicine Research Centre, 14-17 September 2008, Natal, Brazil.

Jenefer Blackwell, "Toxoplasma Centennial Congress – From Discovery to Public Health Management", 21-24 September 2008, Buzios, Brazil.

Jenefer Blackwell, "17th International Congress for Tropical Medicine and Malaria", 29 September – 3 October 2008, Jeju Island, South Korea

Jenefer Blackwell, Joint meeting Brazilian and Indian NIH Tropical Medicine Research Centres, Co-convenor and Speaker, 2 October 2008, Jeju Island, South Korea.

Jenefer Blackwell, Australian Society for Immunology WA Branch "Perth Immunology Group" meeting, 9-10 October 2008, Flying Squadron Yacht Club, Nedlands, WA.

Division of Molecular Biotechnology

Allergens Group

Advances in medical research are highly dependent on having the right tools for the job. An outstanding problem which encompasses most of work of the Division of Molecular Biotechnology is to determine how immune responses to allergens and other inhaled lead the development of allergy and asthma. While fundamental immunology continues to define the important elements and pathological consequences of activating the immune system most of these result from interactions of receptors with specific antigens and are highly dependent on the doses of the antigens and the context in which they are presented. It is therefore not surprising that studies undertaken with the undefined extracts of allergen sources have produced a myriad of results with little agreement between investigators and little potential for knowledge-based interpretations. The essence of the work of Molecular Biotechnology has been to tackle this disconnect by incorporating both the production of defined allergens and antigens and their use for immunological investigation within the one research group.

The specific research areas have concentrated on:

1) determining the immune responses to allergens with varying potency and from different sources to elucidate the differences between responses that lead to allergy and responses that do not,

2) the development of improved immunotherapy with molecularly defined allergens and molecularly engineered derivatives of allergens, and 3) the study of other mucosal immune responses that could influence asthma pathogenesis, especially to microbial antigens.

House dust mite allergy has remained the main focus since it is the most important cause of allergy worldwide and is especially dominant in Australia. New methods of immunotherapy with adjuvants are being explored in mice made allergic to the house dust mite allergen homologue papain. Allergy to cats is being studied because it has been revealed that although the final outcome is an immediate hypersensitivity reaction the sensitisation process is quite different to that of the house dust mite. The study of responses to other mucosal antigens has examined responses to common mucosal colonising bacteria ***Haemophilus influenzae*** *and* ***Streptococcus pneumoniae*** *and in mice* ***Pasteurella pneumotropica*** *in combination with papain allergy.*

***Inflammation Group*:**

Members of the Inflammation Research Group are elucidating the mechanisms by which the UVB wavelengths in sunlight can modulate immune responses, particularly those associated with asthma development. 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, track them and determine 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. We have been focussing on CD4+CD25+ cells in the draining lymph nodes. They have increased activity and gene arrays and functional studies suggest that this is by increased production of interleukin-2. 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 altered cells which in turn would be attracted back to the inflamed skin site. However, as a homeostatic or compensatory response, these cells have reduced immune potential.

Members of the Inflammation Research Group also study 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 2008, the regulatory function of suppressor of cytokine signalling-1 (SOCS-1), a molecule rapidly induced

by interleukin-4 and lipopolysaccharide and perhaps representing an important mechanism of control by interleukin-4, has been studied. Monocytes and macrophages were infected with a SOCS-1-encoding virus and the inflammatory mediator production by these infected cells examined. Studies to examine the anti-inflammatory properties of SOCS-1 and other similar proteins are continuing in human blood monocytes.

Allergy and Immunology Group

Aberrant antibody responses to allergens and bacterial antigens in children during asthma exacerbations and convalescence

B. J. Hales, L. Pearce, L. A. Hazell, W. Smith, W. R. Thomas with Dr A. C. 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 antibody responses to house dust mite allergens of children admitted to 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 antibody to the major Der p 1 and 2 allergens. Children recruited with exacerbation however had an almost complete absence of IgG1 and IgG4 antibody and this was further reduced in the children with persistent asthma or frequent episodes. There was no restoration of IgG antibody after convalescence although the IgE antibody to the allergens decreased. 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. Like the allergens the IgG anti-P6 titres were low in the children with exacerbations and lowest in those with persistent asthma or frequent episodes. Exacerbations associated with rhinovirus infection only had quantitative differences in the antibody responses to children without infection although some of these such as more rapid reductions of IgE titres could be fruitful avenues of investigation. The results show susceptibility of allergic children to asthma exacerbation is associated with defects in anti-microbial and anti-allergen responses.

Development defects in antimicrobial immunity in asthma

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

Antibody titres to the protective P6 antigen of the mucosal colonising bacteria ***Haemophilus influenzae*** were found to develop slowly in pre-school aged children destined to become atopic. Importantly the developmental defect was evident at 2 years of age and thus preceded the development of allergy. This combined with the low IgG antibody titres to P6 of children with frequent and persistent asthma provides a measure of generally altered immune responses and a prognostic marker of children at risk of developing allergy and asthma. Detailed investigation is required to determine the causal relationships of the association. It has now been shown that reduced IgG antibody titres are also found for virulence-associated protein antigens of ***Pneumococcus pneumoniae*** as well as another protective antigen of ***H. influenzae***, P4.

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 a challenge with allergen had increased

resistance to the infection and made higher IgG antibody responses including the Th1 dependent subclass. The bacterial infection also prolonged the eosinophilia found in the lungs.

Antibodies to rhinovirus antigens

B. J. Hales, S. C. Lee, L. A. Hazell, W. Smith, T. K. Heinrich with Dr I. A. Liang and Professor P. N. LeSouef, and Dr C. M. Hayden UWA School of Paediatrics and Child Health.

Rhinovirus infection frequently exacerbates asthma and may have a role in the development of sensitisation. Immunological studies have however been limited partially because of the lack of suitable antigens and antibody assays have been limited to measuring the largely isolate-specific neutralising antibodies. While neutralising antibodies are important for the development of resistance to reinfection with the same serotype it is likely that the bulk of the immune response and its accompanying immunopathological effects is due to the many antigenic determinants that do not react with neutralising antibodies and are shared by similar isolates. To explore this and test the feasibility of performing antibody-isotype assays the VP1 capsid protein was made as a recombinant polypeptide expressed in ***E. coli***. A representative from the type A and type B families of the rhinovirus was made in the expectation that the 80% sequence identity within each group will allow sufficient cross reactivity to detect responses to the isolates that infect children. Antibody assays with the antigens showed high titre reactions for IgG1 antibody from children and the reactivity to the more ubiquitous type A protein was more frequent than the type B protein. Sera were frequently specific for either the type A or the type B showing a low degree of cross reactivity and the unlikely potential of cross reactivity with even less similar members of the picornoviridae family.

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

Although it probable that the major cat allergen Fel d 1 is the target of most of the IgE binding activity of cat dander there evidence for frequent IgE binding by other unidentified allergens especially from salivary proteins. The contribution of these allergens to allergic response to the cat is unknown and may be particularly relevant for people with rhinoconjunctivitis who have been shown in three independent studies to have low IgE titres to the major allergen Fel d 1. Previous analysis of cDNA libraries from different cat tissues has revealed the salivary lipocalin Fel d 4, which has frequent but generally low IgE binding. In addition to these allergens a number of other potential cat allergens have now been tested for IgE and IgG antibody binding. These include cat albumin aka Fel d 2, the cystatin Fel d 3 allergen, the breast and salivary expressed (BASE) protein, haptoglobin and S100A12.

The new IgE binding proteins were identified from IgE screening assays or in the case of BASE its homology with a major horse allergen. The folding of recombinant allergens was authenticated by circular dichroism. The most important allergens were Fel d 1, Fel d 4 and Fel d 2. For most of the sample representing predominantly adults with rhinoconjunctivitis the titres to Fel d 1 and Fel d 4 were similar although a minority (8%) had high titres to Fel d 1. Very high titres of IgG1 antibody were consistently detected which on average were higher in the non-allergic group. No IgG1 antibodies to the other IgE-binding proteins were detected whereas for the bulk of the subjects, the IgG4 antibodies to Fel d 1 and Fel d 4 were similar and higher in allergic subjects. The less potent allergens were not reactive. These results not only show the significance of Fel d 4 in addition to Fel d 1 but contrast markedly to mite allergy where IgG antibody is restricted to allergic subjects and the relative presence of the different IgG subclasses is the same for all allergens.

Bystander allergy and 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 intranasal administration of activated 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 but this was largely dependent on the use of activated papain.

Similar desensitisation with greatly diminished lung pathology could also be achieved by sublingual administration of non-activated papain provided that it was absorbed to chitosan nanoparticles. The administration of the activated papain with Der p 2 was found to produce lasting allergic responses to Der p 2 instead of the usual transient reactions.

Anti-microbial peptides

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

Acinetobacter baumannii is an important cause of infection of intensive care patients such as burns victims. It is of major concern because it has an intrinsic ability to develop antibiotic resistance and some isolates are resistant to all of the antibiotics 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 peptides or peptides based on their structural motifs. Here we have used a phage display 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 bacteria and archea 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. Peptides were active when they were synthesised as proteolytic resistant retroinversopeptides and many had low toxicity for human cells. The peptides were shown to have varying mechanisms of action as demonstrated by their bacteriocidal and membrane depolarision activities. Clinical isolates resistant to the standard antibiotics were susceptible.

Inflammation Group

Immunomodulatory effects of UVB radiation on inflammatory airways disease in mice

PH Hart, S Gorman, JP McGlade, M Lambert, M Judge, DH Strickland

UVB immunomodulatory effects have been implicated not only in allowing skin cancer development but also in the control of immune-driven diseases, such as autoimmune and infectious diseases, in both experimental animals and humans. We have analysed the effect of a single exposure to UVB (for a time equivalent to about 20 minutes in noon in summer in Perth) on two asthma models in mice.

In the first model, mice were UVB-irradiated on their shaved backs three days before sensitisation, resensitisation and challenge intranasally with the cysteine protease, papain. In the second model, mice were irradiated on their shaved backs three days before sensitisation, and resensitisation, 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 as we can transfer the regulatory effects of UV into naïve mice by transfer of lung-draining lymph node cells from UV-irradiated mice. We are seeking the identity of these regulatory cells and their mechanism of action. These studies will contribute to a basic understanding of the immunological events in asthma development and how they can by modified by UV irradiation of skin.

Funded by NHMRC

Comparative effects of UVB irradiation and vitamin D3 on murine asthma models

S Gorman, PH Hart, M Judge

Upon irradiation of skin 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 levels of 1,25 $(OH)_2$ vitamin D3 produced by keratinocytes and immune cells at the irradiated site may be involved in the immunomodulatory effects following acute UV exposure of skin. Hence we have studied the effects of 1,25 $(OH)_2$ vitamin D3 applied directly to skin. The concentration of 1,25 $(OH)_2$ vitamin D3 was 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 erythemal UVB exposure. Both UVB and application on skin of 1,25 $(OH)_2$ vitamin D3 can enhance the regulatory capacity of non-antigen-specific CD4+CD25+ cells in the draining lymph nodes. When purified from these nodes, and transferred into allergen-presensitised mice, the immune responses in the airways to aerosolised allergens is reduced. These results suggest that 1,25 $(OH)_2$ vitamin D3 formed upon UV irradiation of skin may contribute to the immunomodulatory effects of UV irradiation of skin, as well as the enhanced health of our immune system, and in particular the immunoregulatory properties of innate CD4+CD25+ T regulatory cells such that they can modulate the immune responses associated with asthma.

Funded by Cancer Council WA and NHMRC

Immunomodulatory effects of vitamin D3

S Gorman, M Judge, PH Hart

We have been investigating how 1,25 $(OH)_2$ vitamin D3 is immunomodulatory. We have been studying the expression of mRNA levels for cells, both CD4+CD25+ and CD4+CD25- cells, isolated from the nodes draining skin where 1,25 $(OH)_2$ vitamin D3 had been previously applied. We have also studied the expression of molecules by gene arrays, and valided many of the findings by Real-time PCR and by studies of protein expression. Many interesting candidate molecules have been identified that may contribute to the increased regulatory properties of CD4+CD25+ cells from mice painted on their skin with 1,25 $(OH)_2$ vitamin D3. The potential of 1,25 $(OH)_2$ vitamin D3 to regulate ***in vitro*** the activity of CD4+CD25+ and CD4+CD25- cells has also been investigated and have suggested that when painted onto skin, the effect of 1,25 $(OH)_2$ vitamin D3 on CD4+CD25+ cells is probably indirect by the actions of dendritic cells or mast cells. These studies are ongoing.

Funded by Cancer Council WA and NHMRC

Effect of UVB on bone marrow-derived dendritic cells

PH Hart, S Gorman, M Judge, R McKeone

In response to erythemal 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 oedemal 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 erythemal UV irradiation of skin as we hypothesise that some of the systemic effects of erythemal/oedemal 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.

Funded by NHMRC

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

PH Hart, CM Prêle, 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. Adenoviral vectors have recently allowed transduction of a high percentage of human macrophages. We have been studying the mechanisms by which monocytes/macrophages are activated and then how interleukin-4 (IL-4) can 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 but the mechanism of regulation was not known. In 2008, we published by detailed biochemical analyses that SOCS1 regulates the Interferon but not the NFκB pathway in TLR-stimulated human monocytes and macrophages. 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.

Funded by NHMRC

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Staff and Students (Inflammation Group)

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Shelley Gorman BSc (Hons) PhD

Cecilia Prêle BSc (Hons) PhD, until October 08

Melinda Judge BSc (Hons)

Misty Lambert BSc (Hons)

Richard McKeone BSc, PhD qualifying, until November 08

Jacqueline McGlade BSc (Hons), PhD from September 08

Postgraduate Students

Jacqueline McGlade BSc (Hons), ***PhD Candidate until August 08***

Eleanor Woodward BSc (Hons), ***PhD Candidate***

Jacqueline Bisley BSc, ***Hons Candidate***

Invited Presentations

W. R. Thomas. Early aberrant antibody responses of aeroallergen sensitised people to subclinical bacterial infection. 27th Symposium Collegium International Allergologicum, Curacao

Prue Hart. Invited symposium speaker, Australian Society for Dermatology Research, Sydney, May 2008

Prue Hart. Invited Seminar, Centenary Institute, University of Sydney, July 2008.

External Committees

W. R. Thomas. NHMRC Program grants review panel

W. R. Thomas. International Allergen Nomenclature Committee

Awards

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

Shelley Gorman. Adjunct Senior Lecturer 2008-2011, Richard Walter Gibbon Medical Research Fellowship, University of Western Australia, Faculty of Medicine and Dentistry, 2008.

Jacqueline McGlade. PhD with Distinction, University of WA

Division of Population Sciences

The Division of Population Sciences is the largest Division at the Institute and has grown in recent years to almost 200 staff and students.

The Division is made up of multi-disciplinary teams consisting of epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists. These research teams work collaboratively with government, corporate, non-government and community groups in a wide range of research interests related to child health and development.

The Division investigates a wide range of burdensome conditions that affect the developmental health of children. These include: low birth weight, behavioural and mental health problems, autism, obesity and infection.

Many projects utilize linked population databases to identify patterns and trends of morbidity and mortality and have explored new ways of measuring and analysing the important influences in whole populations of children, their families and communities. More specifically, the Division strives to develop preventive strategies that promote and maintain the health and development of children in addition to their social, emotional, academic, and vocational wellbeing.

Highlights:

For the researchers within the Division of Population Sciences, 2008 has been another busy year. The following are a selection of key highlights from this year:

[1] In December 2008 our researchers found that children whose mothers were stressed during pregnancy are at higher risk of developing behavioural and emotional problems. Data from more than 1700 children enrolled in the Western Australian Pregnancy Cohort (Raine) Study were analysed.

The Raine Study is a longitudinal study that began in 1989 by recruiting nearly 3000 women at around 18 weeks of pregnancy. Pregnancy data was collected at King Edward Memorial Hospital. Follow-up data continues to be collected at the Telethon Institute for Child Health Research.

Report co-author Monique Robinson, a research officer and PhD candidate within the Division, found that maternal smoking, low income during pregnancy, multiple 'baby blues' symptoms after birth and stress were each associated with poorer behavioural and emotional outcomes in preschool children. The risk was also higher in children of non-Caucasian mothers and those who breastfed for

shorter durations.

[2] In October 2008, Disability Researcher, Dr Helen Leonard attended the World Rett Syndrome Congress held in Paris, France to showcase the benefits and future potential of an internet tool known as InterRett. The internet is emerging as a valuable tool for scientists to gather data for critical research into rare diseases such as Rett Syndrome.

The InterRett online database had greatly expanded research into the neurological disorder Rett syndrome, which affects 1 in 8500 girls. The Congress focused on potential new therapeutic options and the best way to undertake clinical trials where these and other therapies can be assessed.

In July 2008, Dr Leonard was awarded an International award known as the "Circle of Angels Research Award" at a conference in Chicago, USA for her contribution to major advancements in the understanding of the neurological disorder Rett syndrome.

Dr Leonard was honoured for her substantial scientific contributions which have not only increased the understanding of Rett syndrome at basic levels but have helped define the Rett syndrome phenotype and clinical outcomes.

[3] In August 2008, Institute researcher Melissa O'Donnell and Professor Fiona Stanley, Director of the Telethon Institute for Child Health Research in their publication in the Australian and New Zealand Journal of Public Health called for a new approach amid rising rates of abuse notifications and children being brought into State care. As the report co-authors they say that a greater focus is needed on preventing abuse and neglect occurring in the first place.

Their paper called for a real commitment to protect all children by supporting families and children before they reach the point of being abused and neglected. The current approach to child abuse in Western Australia has done little to prevent abuse but focuses on intervening once much of the harm has already been done. Australia is seeing an unprecedented increase in the rate of child protection notifications and children being taken into care – doubling in the past decade.

The purpose of the paper was to highlight the issue of child abuse and call for governments to take a prevention focus rather than an acute reactive focus. The paper calls for child abuse and neglect to be tackled in the same comprehensive way as other serious health issues have been

addressed such as smoking or coronary heart disease -- that is to identify the risk factors, promote a range of interventions and change community attitude.

[4] In July 2008, Professor Colleen Hayward was honoured as the 2008 National NAIDOC Person of the Year. Professor Colleen Hayward was the Manager of the Institute's Kulunga Research Network, which aims to build capacity within the Aboriginal community to undertake and influence research.

This award is a significant national achievement for Colleen and she has been a key figure in pushing for policy in Indigenous health and wellbeing that is based on real evidence about what will really improve outcomes for Aboriginal children in particular. NAIDOC originally stood for 'National Aborigines and Islanders Day Observance Committee', but now its acronym has become the name of the week itself.

[5] In June 2008, Population Sciences researcher Therese O'Sullivan concluded that something as simple as adding a banana to your bowl of cereal and milk could be the key to better mental health in teenagers. Therese presented her research at the Dietitians Association of Australia (DAA) national conference announcing that based on her research, a high quality breakfast, with foods from at least three different healthy food groups, was linked with better mental health in 14 year old boys and girls.

And she said that for every extra food group eaten at breakfast, the associated mental health score improved.

Divisional researchers asked over 800 teenagers in the Raine Study what they ate for breakfast, and scored this based on their intake of the core food groups. Mental health was assessed using a child behaviour checklist. They found that just one in four teens ate a high quality breakfast, and the two most common core food groups eaten at breakfast were breads/ cereals and dairy products.

[6] A study by researchers in the Division of Population Sciences published in May 2008 found that swimming pools in remote Aboriginal communities can dramatically reduce rates of skin, ear and chest infections. Seven years of clinical records at two communities, Jigalong and Mugarinya, in Western Australia's Pilbara region were examined. The research team, headed by Associate Professor Deborah Lehmann had access to records of 131 children in Jigalong and 128 children in Mugarinya. The analysis revealed that infections were more than halved in

both communities.

Skin infections are of major concern because they can lead to chronic heart or kidney disease later in life. These diseases are very common in Aboriginal communities. Middle ear infections (otitis media) can lead to hearing loss that can affect schooling and hence opportunities later in life. Chest infections are the most common infection for which young Aboriginal children are admitted to hospital.

This research provided important evidence that swimming pools can have significant health benefits in remote communities.

The study found that not only have the children benefited by fewer visits to the clinic for infections, but the swimming pools in communities had also reduced the workload in the local clinics and cut down costs of treatment with antibiotics.

[7] In May 2008 results published in the ***Medical Journal of Australia*** *found a strong link between childhood ear infections and exposure to tobacco smoke.*

The families of 100 Aboriginal children and 180 non-Aboriginal children participated in the Kalgoorlie Otitis Media Research Project, allowing the collection of social, demographic, environmental and biological data to investigate the causes of otitis media (middle ear infections). The children had regular ear examinations from birth until 2 years of age.

Chief Investigator Associate Professor Deborah Lehmann, who heads the Division's infectious diseases research found that those children who were exposed to environmental tobacco smoke had a greater chance of suffering from otitis media compared to those children who were not exposed. The results highlight the importance of reducing children's exposure to passive smoking, and this is particularly important for Aboriginal people where the rates of both smoking and otitis media are high.

Ear infections are the most common reason that young children see a doctor and can cause life-long problems. Up to 20 per cent of children have more than three ear infections before 1 of age. If their hearing is damaged, it can seriously affect their educational outcomes and social circumstances in adulthood.

In Aboriginal children, these ear infections typically start at a younger age, are much more common and more likely to result in hearing loss.

Key findings from the project include:

a) Otitis media was diagnosed at least once in 74% of Aboriginal children and 45% of non-Aboriginal children.

b) 64% of Aboriginal

children and 40% of non-Aboriginal children were exposed to environmental tobacco smoke.

c) If we eliminated exposure to tobacco smoke we estimate that we could reduce ear infections by 27% in Aboriginal children and 16% in non-Aboriginal children.

d) The impact of passive smoking in the home on ear infections was reduced if the children also attended day care.

[8] Also in February 2008, research findings from the world's largest study on language emergence conducted within the Division revealed that one in four late talking toddlers continue to have language problems by age 7.

The LOOKING at Language project has analysed the speech development of 1766 children in Western Australia from infancy to seven years of age, with particular focus on environmental, neuro-developmental and genetic risk factors. It is the first study to look at predictors of late language.

The LOOKING at Language project has analysed the speech development of 1766 children in Western Australia from infancy to seven years of age, with particular focus on environmental, neuro-developmental and genetic risk factors. It is the first study to look at predictors of late language emergence at 24 months.

The findings were published in the February edition of Journal of Speech, Language and Hearing Research and signalled mixed news for parents worried about their child's language development.

The study has found that while a late start doesn't necessarily predict on-going language problems, most school aged children with impaired language were late talkers. This indicates the value of having late talkers evaluated by a speech pathologist and have their hearing checked. Early intervention has been shown to assist greatly with a child's language development.

Co-Chief Investigator Associate Professor Kate Taylor commented that the next challenge for researchers was to find ways to identify which children were likely to outgrow the problem so that interventions could be targeted at those in need.

Other findings from the LOOKING at Language project have included that a mother's education, income, parenting style or mental health had no impact on a child's likelihood of being a late talker.

[9] In January 2008, Deputy Prime Minister Julia Gillard, Minister for Families, Housing, Community Services and Indigenous Affairs Jenny Macklin, Professor Fiona Stanley and Professor Colleen Hayward attended the Perth launch

of the Indigenous Australian Early Development Index (I-AEDI) which was developed by the Kulunga Research Network within the Division of Population Sciences.

The I-AEDI project has involved the adaptation of the highly successful Australian Early Development Index to ensure it takes into account cultural differences in child development. The Index is a teacher-completed checklist of over 100 questions, which measure five key areas of development as children enter their first year of school: physical health and wellbeing; social competence; emotional maturity; language and cognitive skills; and communication skills and general knowledge.

The project has received funding from Shell Australia and the Federal Government's Department of Education, Employment and Workplace Relations (DEEWR).

The I-AEDI is a tool that helps show where the focus of strategies should be and identifies what the vulnerabilities are for children in specific communities and then what services needs to be in place to address those vulnerabilities.

The Index has the potential to set a benchmark against which the effectiveness of strategies and interventions could be measured. The I-AEDI will enable communities and schools to monitor how their children are doing at this critical stage in their learning career. This will mean that preventive action can be based on solid evidence as to what the local needs are and what strategies will be most effective.

Aboriginal Health Research

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

Professor Colleen Hayward, Marita Smith, Daniel McAullay, Heather Monteiro, Tracey-Lee Edwards, Associate Professor Dawn Bessarab, Theresa Venz

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.

Two projects were initiated following the release of the Report. Project One, sought to better understand, through stories from Aboriginal parents and family members about other things that maybe happening within the family and the community that may have been a factor in the death of an infant, child or young person. The second project was to develop a communication and dissemination strategy, specifically targeted for the Indigenous community using the information from the Report, as

well as appropriate strategies for dealing with difficult issues linked to the Report.

A series of fact sheets for service providers, Aboriginal community groups, families and individuals were developed by the Kulunga Research Network in consultation with the Aboriginal Health Council of Western Australia (AHCWA) and specifically with Aboriginal Health Promotion Development Officers from across the state.

The fact sheets were then disseminated to the community through a series of workshops held in Geraldton, Kalgoorlie and Perth. This project has provided Aboriginal communities around the State with access to resources that can be used to inform health promotion activities which address the critical issues identified in the Report at their local level.

The consultation process identified gaps in resources addressing the critical issues and recommendations to key organisations of these gaps provided as a basis of future action;

The project is funded by the WA Department for Child Protection's 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.

The project is funded by the NHMRC (Program Grant)

Evaluation Framework and Research Plan for the BHC Onslow Leaping Lizards Project

Dr Roz Walker, Dr Clair Scrine, Glenn Pearson.

The project aimed to develop an Evaluation Framework to enable the assessment of the school based intervention (Leaping Lizards) being implemented in Onslow under the Building Healthy Communities in Remote Australia funding initiative.

Preliminary discussions took place between the project team and the program coordinator and local project officer to develop an Evaluation Framework and the collection of baseline data to assess the current status of health, and wellbeing of different population groups within the Onslow community. However, staff changes within the Division of General Practice and the program and the selection of the Leaping Lizard program as part of a broader ***Australian Better Health Initiative*** (ABHI) evaluation site resulted in an agreed decision to discontinue the project in early 2008.

This project is funded by the Pilbara Division of General Practice

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 have been published in the Medical Journal of Australia.

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

Indigenous Mental Health Textbook

Dr Roz Walker, Pat Dudgeon (UWA Indigenous Studies Centre)

This project aims 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 being developed by clinicians, cultural and educational experts. The resource will have applicability across Indigenous Australia. Several chapters have been completed and it is expected that the remainder will be completed by late April and pilot-test in universities and training colleges throughout Australia for use in 2010

The textbook will enable practitioners to understand the historical and contemporary influences and social determinants on Indigenous social and emotional wellbeing and the impact on mental health policy directions. It will incorporate specific clinical mental health assessment processes and culturally appropriate treatment interventions. Several staff at the Institute are contributing to the Textbook. Professor Sven Silburn is completing a Chapter

on Preventing Suicide in Indigenous populations. Professor Steve Zubrick is co-authoring two chapters with Dr Roz Walker – one on the policy context of Indigenous mental health and the second on the social determinants of Indigenous mental health. Dr Roz Walker and Dr Chris Sonn have completed a Chapter on Being a mental health Practitioner. Michael Wright completed a Chapter on social and cultural contexts of Indigenous Mental Health.

An editor will be engaged to ensure that a quality, readable and publishable resource is produced to assist students and other key stakeholders to understand the 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 TICHR/Kulunga staff engaged as consultants by the Australian Council for Educational Research (ACER)

Job aspirations for Indigenous young people in the East Kimberley

Dr Roz Walker, Dr Clair Scrine, Carrington Shepherd

This project was commissioned by East Kimberley Job Pathways (EKJP), a subsidiary of the Wunan Foundation Inc., in early 2007 to identify the study and career aspirations of Aboriginal young people. This qualitative research project engaged with Indigenous young people in the region and asked about their aspirations, motivators, barriers and overall views toward employment, both locally and out of the region. The research findings have been comprehensively documented in a report subtitled, "Making New Tracks". It reveals a range of external factors that impede the formation and realisation of Indigenous young people's job aspirations and goals and limit their capacity to maximise available opportunities.

The report findings and recommendations were disseminated to key stakeholders in the region.

This project was funded by the Wunan Foundation Inc

Rio Tinto Aboriginal Health Partnership – Strong Foundations, Sustainable Futures

Professor Colleen Hayward, Heather Monteiro, Tracey-Lee Edwards ,Dr Clair Scrine, Gail Barrow, Terry Boyle, Jackie Goldfinch, Theresa Venz

The Rio Tinto Aboriginal Health Partnership (RTAHP) commenced in July 2008 and will continue for a period of two years. The Partnership aims to bring about improvements in the area of Aboriginal child and maternal health. It seeks to do this through a specific project whose activities will address some of the training, development and support needs of Aboriginal Health Workers in three key regions in Western Australia (WA).

The regions in Western Australia are Karratha, Roebourne and Tom Price in the Pilbara, Kununurra and surrounding areas in the East Kimberley, and Kwinana in the South Metropolitan area of Perth.

The Rio Tinto Aboriginal Health Partnership builds on the outcomes and relationships developed during a previous five year Aboriginal maternal and child health partnership between Rio Tinto and the Telethon Institute for Child Health Research known as the Rio Tinto Child Health Partnership (RTCHP).

In particular, the project is based on the RTCHP's recognition of the critical role Aboriginal Health Workers play in meeting the complex health care needs of Indigenous people, and the range of workforce development issues faced by Aboriginal Health Workers.

Specifically, the project is seeking to address the need for capacity building initiatives and on-site skills training for Aboriginal Health Workers to support their career pathways and ensure they feel empowered, capable and confident.

The objectives of the Rio Tinto Aboriginal Partnership Project are:

1. To enhance the professional development opportunities for Aboriginal community health workers;
2. To increase awareness and build the capacity of Aboriginal Health Workers, Aboriginal Community Controlled Health Organisations and the Aboriginal community to bring about improvements in the area of Aboriginal child and maternal health;
3. To assist WA Aboriginal community based health organisations to work towards sustainability; and
4. To encourage governments to endorse the resources developed as a result of the Project and following its completion, take responsibility for further implementation across the State.

The Rio Tinto Aboriginal Health Partnership comprises Rio Tinto and the Telethon Institute for Child Health Research through the Kulunga Research Network.

This project is funded by Rio Tinto.

Whole of Government Strategic Framework for Indigenous Generational Change

Dr Roz Walker, Carrington Shepherd

The Kulunga team contributed to the development of a comprehensive whole-of-government and community policy Framework to addresses the particular

needs of Indigenous people in Western Australia. 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. The framework developed for consideration by the Committee 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.

ARACY Evidence in Action Topical Paper

Carrington Shepherd, Dr Roz Walker.

Engaging Indigenous Families In Preparing Children for School: This topical paper was commissioned by the Australian Research Alliance for Children and Youth (ARACY) as resource for Communities for Children (C4C) practitioners. It provides C4C Managers with practical, evidence-based approaches of what works, why it works and strategies that ought to be implemented to improve the services that cater for the well being of Aboriginal young children and their families. It examines the complexities associated with C4C program delivery and builds on the previous ARACY Evidence into Action Topical Papers. This paper addresses elements of the pathways to school readiness, positive transition factors and the engagement and involvement of Aboriginal parents in working with their child within the systems currently available in early learning and care. A webinar and power point were also presented nationally.

This project was funded by ARACY

From the ground up: Working with communities in the South West

Professor Colleen Hayward, Jason Barrow, Gail Barrow, Carrington Shepherd, Terry Boyle

This project, 'From the Ground Up - Working with communities in the South West', will be undertaken over three years from January 2008 until December 2011. It will involve the Kulunga Research Network (Kulunga) working in partnership with Alcoa to implement a range of targeted activities to build capacity amongst Alcoa staff and the Aboriginal communities in the Peel and South West regions of Western Australia.

The proposal complements and supports Alcoa's social investment strategy, internationally and in Australia, which regards people as their most valuable asset, is committed to equal opportunity for women and places a particular focus on improving the lives of Indigenous people (Alcoa in Australia).

The proposal also addresses the Alcoa 'Safe & Healthy Children and Families' portfolio in the following ways:

- encouraging/supporting Alcoa staff to participate in cross-cultural training which will enhance their competence in promoting greater Indigenous participation in local community activities designed to promote safety and health outcomes through their active involvement and mentorship;
- developing the capacity of all children, young people, individuals and families through their engagement in existing and new community based initiatives; and
- developing capacity in communities by acknowledging and promoting Indigenous cultural strengths

This project is funded by Alcoa Australia

Awareness and impact of the 'Make Smoking History' advertising campaign among Aboriginal smokers in Western Australia

Professor Colleen Hayward, Heather Monteiro, Glenn Pearson, Carrington Shepherd, Marita Smith, Peta Gooda, Stephanie Hall, Terry Boyle

Anti-smoking mass-media campaigns have been shown to reduce smoking prevalence in the mainstream community. It is unclear, however, if these campaigns have any affect on Aboriginal smokers. The aim of this study was to evaluate the awareness and impact of a mainstream mass media advertising campaign on Aboriginal smokers in Western Australia.

The evaluation was carried by the Kulunga Research Network team in July 2008, and took place in three sites (the Perth metropolitan area and the non-metropolitan towns of Kalgoorlie and Broome) to provide a broadly representative mix of metropolitan and non-metropolitan participants. Participants were asked about their awareness of the advertisements in the campaign, whether they found them believable and relevant, and the impact the advertisements had on their smoking behaviour.

The results suggest that this particular anti-smoking mass media campaign was effective in reaching Aboriginal smokers. The majority of the participants interviewed had seen the television advertisement and/or heard the radio advertisement, although there was considerably greater awareness of the former. Both forms of advertising were

considered to be believable and relevant by the majority of Aboriginal smokers. Most of the smokers interviewed thought about cutting down and/or quitting after seeing or hearing the advertisements, however very few had successfully quit in the two months prior to the study interview. More needs to be known about what motivates Aboriginal smokers to quit, or to not smoke at all. A better understanding of these motivations may lead to more effective cessation interventions and mass-media campaigns.

This project was funded by the Cancer Council WA

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 an innovative approach to empower communities, schools and families in supporting healthy child development. The Institute provided the psychometric analysis for the adaptation and validation of the original Canadian index for use in Australia. This research has been carried out in partnership with the Centre for Community Child Health in Melbourne and the Offord Early Childhood Studies Centre in Canada.

Following the success of the first phase of national AEDI project (2005-7) the Australian Government engaged the AEDI national partnership to roll-out the AEDI to every Australian community in 2009. This will in effect be the first national census of the developmental outcomes of children at age 5 years conducted anywhere in the world.

The AEDI provides communities with a tool to focus attention on how their 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 and governments to monitor and evaluate early childhood programs and interventions.

The support of the Institute has also enabled the further development of the AEDI instrument and its school administration process so they are more culturally inclusive of Indigenous children and those with language backgrounds other than English.

This project is funded by the Department of Education, Employment and WorkPlace Relations – Australian Government and Shell Australia Ltd

Starting on Track: The Pilbara AEDI Initiative

Dr Roz Walker, Carrington Shepherd.

The Starting on Track project involved the implementation of the AEDI in Hedland and Newman and surrounding areas. The project was funded through the partnership with BHP Billiton Iron Ore Health Partnership. Subsequently, the Project leader secured supplementary funding from a range of additional sponsors to implement the AEDI in 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.

The project provided:

1. baseline data on the strengths and vulnerabilities of pre-primary age children in across the Pilbara
2. 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
3. establishment of Early Years Action Groups
4. reorientation of Communities for Children community partner programs in the West Pilbara; and
5. direction to the BHP Billiton Iron Ore Community Investment Program 2010-2014

This project was funded by BHP Billiton Iron Ore Health Partnership 2006-2009 & various sponsors.

The Indigenous Australian Early development Index (I-AEDI) Project

Professor Sven Silburn, Sally Brinkman, Professor Colleen Hayward, Sue Ferguson-Hill, Elizabeth Cromie, Adele Austin, Tracey-Lee Edwards, Dr Roz Walker, Gail Barrow

The Indigenous Australian Early Development Index (Indigenous-AEDI) project, managed by the Kulunga Research Network, has adapted the widely used Australian Early development Index (AEDI) to ensure it identifies and takes into account Aboriginal cultural differences in the influences on child development.

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 measurable 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.

The first phase of the adaptation process involved qualitative investigation with

Indigenous teachers and other Indigenous school personnel, parents and community members, and quantitative analysis of the psychometric characteristics of the AEDI. The analysis was undertaken on data for 1,474 Indigenous children and 30,087 non-Indigenous children collected in the first phase of the rollout of the AEDI. These findings were used to inform the adaptations needed for a trial adapted Indigenous version of the AEDI in pilot sites in Western Australia.

The adapted Indigenous version of the AEDI was piloted in the second school term of 2008 with Indigenous children from 49 schools in three sites around Western Australia. Following further evaluation, the transferability of the adapted Checklist will be tested in 2009. The process of undertaking the adapted AEDI Checklist with the joint collaboration of a teacher and a cultural consultant within the school was also evaluated and has become the recommended standard process of AEDI checklist completion for Indigenous children.

Each community's results are reported back on a community-by-community basis to provide locally relevant planning data and evidence for the resources needed to enable better early child development outcomes, and to build on community strengths. It also provides valuable data for schools to better meet the learning needs of their Indigenous students

An important aim of the project is to build sustainable community capacity within the trial sites. Working with the community in using the local findings to mobilise community act ion, and advocacy for identified service needs is a key component of the Indigenous AEDI process.

At the beginning of 2009, the I-AEDI project extended to the Northern Territory the AEDI and the recommended process of checklist completion for Indigenous children is being implemented in three regional and community sites. These sites will also be testing improvements to the community dissemination processes in Indigenous communities following an analysis of the 2008 pilot in Western Australia.

The project also aims to build community capacity by transferring research skills through the training and employment of local people in the project, raising awareness of the importance of early child development, identifying the availability and effectiveness of local services for children and families, and empowering Aboriginal communities with high quality local data which can be used in proposals and planning for family and child development programs and services.

This project was funded by Shell Australia, Department of Families, Community Services and Indigenous Affairs (Australian Government).

Staying on Track: Reducing Substance Misuse for Aboriginal Young People in Port Hedland and Newman

Dr Roz Walker, Carrington Shepherd.

The Staying on Track is the second project funded through the BHP Billiton Iron Ore Health Partnership Agreement. The project lead, Dr Roz Walker has been involved in a participatory action research process working with young people and key stakeholders in Newman, Hedland and surrounding communities to address to identify and develop innovative preventative programs to address these issues. Carrington Shepherd and Roz Walker produced a customised report of the Western Australian Aboriginal Child Health Survey (WAACHS) findings for this region. This report indicates that 27% of Aboriginal young people reported high levels of alcohol use, 24% reported marijuana use. Issues of mental health, social and emotional wellbeing and suicide are also a concern within the Region. The team was also successful in obtaining additional funding through the Criminal Property Confiscation 2002 Act to implement a range of interventions. An evaluation will be undertaken with young people to assess the effectiveness of these interventions in empowering young people, their decision-making around substance misuse and social and emotional wellbeing. This project was showcased at the National ARACY Think Tank on involving young people in research Sydney in November.

This project was funded by BHP Billiton Iron Ore Health Partnership 2006-2009 and Criminal Property Confiscations Act 2002 Funding 2008.

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.

Associate Investigators: Ms June Councillor, Dr. Julie Owen

Funded by Healthway and aimed to

1. Describe the knowledge and attitudes of Aboriginal women living in the Kimberley and Goldfields regions in WA about alcohol use in pregnancy and its effects on the unborn child
2. Gain insight into current practice of alcohol consumption during pregnancy for Aboriginal women
3. Ascertain support for initiatives to provide women of childbearing age with information about the risks of alcohol consumption in pregnancy

4. Identify the preferred modes of delivery of educational messages

We conducted seven focus groups (four in the Goldfields and three in the Kimberley) with 32 Aboriginal women.

This study showed that Aboriginal women are aware of the adverse effects of prenatal exposure to alcohol.

The participants suggested multiple strategies to support Aboriginal women to not drink alcohol in pregnancy. The results have been reported back to the Aboriginal community in both the Goldfields and the Kimberley region and are currently being written up for publication.

Funded by a Healthway Starter Grant.

Alcohol and Pregnancy: Health promotion for health professionals

C Bower, E Elliott, N Henley, A Bartu, J Payne, C O'Leary, H D'Antoine, K France, R Mutch

The Alcohol and Pregnancy: Health Promotion for Health Professionals project that was funded by Healthway was completed at the end of 2008. The ***Health Professionals Making a Difference Resources*** (a 38 page booklet, A4 fact sheet, wallet cards to give to women and desk-top calendar) were produced by synthesising existing material for health professionals and conducting formative research with health professionals and women. The resources can be viewed and downloaded at www.ichr.uwa.edu.au/alcoholandpregnancy.

The resources were distributed to 3,507 health professionals (Aboriginal health workers, allied health professionals, community nurses, general practitioners, obstetricians and paediatricians) throughout Western Australia (WA) in April 2007. An evaluation questionnaire was mailed to a representative sample of 1,867 health professionals in October 2007 and the data are currently being analysed and compared with data collected from health professionals before the resources were available.

The ***Alcohol and Pregnancy: Health Promotion for Health Professionals*** project has demonstrated the importance of sustaining the resources beyond the term of the project and making them available to health professionals throughout Australia. It is important to continue to raise health professionals' awareness of Fetal Alcohol Spectrum Disorder and have resources available that will impact on their knowledge, attitudes and practice in the prevention of prenatal exposure to alcohol and Fetal Alcohol Spectrum Disorder.

Funded by a Healthway Project Grant and the NHMRC Program Grant

Alcohol and Pregnancy: The association between dose, pattern, and timing of prenatal alcohol exposure and fetal and child outcomes

CM O'Leary PhD studies. Collaborators: Nassar N, Kurinczuk JJ, Bower C, Zubrick S, Taylor CL, Dixon G.

Two papers were completed in 2008 and have recently been published. One was on fetal growth and preterm birth in relation to maternal alcohol consumption in pregnancy, and the other was on language delay in two-year old children in relation to maternal alcohol consumption in pregnancy, demonstrating the importance of dose and timing on risk of exposure. Two further analyses are being undertaken – an examination of child behaviour problems and prenatal alcohol exposure and an analysis of the effect of the method of categorizing prenatal alcohol exposure.

Funded by an NHMRC program grant

Pregnancy outcomes following assisted reproductive technologies (ART)

Hansen M, Colvin L, Petterson B, Kurinczuk JJ, Bower C.

Using record linkage, we investigated hospital admissions during the first 3 years of life for all singleton children born in Western Australia between 1994 and 2000. The analysis was based on 1328 ART infants and 162 350 spontaneously conceived infants. ART infants had a significantly longer birth admission and were four times more likely to be admitted to neonatal intensive care units (NICU) than infants who were spontaneously conceived. ART children also had a 60% increased risk of one or more admissions in their first year, although they were no more likely to be admitted during their second and third years of life. Maternal, infant and socio-economic confounders accounted for most of the increased risk in the first year, but after adjustment, a significant 20% increase in the risk of admission to NICU and admission to hospital during the first year remained. A similar analysis based on twin pregnancies has been submitted for publication.

Funding body: National Health and Medical Research Council of Australia Project Grant #211930 to MH, Principal Research Fellowship #353628 to CB.

Pharmacovigilance in pregnancy using population-based linked datasets

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

Using record linkage of national dispensing data for subsidised prescription medicines to pregnancy events in WA from 2002 to 2005, we identified that dispensed medicines were linked to 28.0% of the pregnancy events.

Multiple birth pregnancies were 50% more likely to be dispensed a medicine in the first trimester. As parity increased, so did the likelihood of a medicine being dispensed in pregnancy. Women who were dispensed a medicine were twice as likely to smoke during pregnancy and were 14% more likely to have had a pregnancy with a registered birth defect. This work has demonstrated that linkage of dispensing data to pregnancy events is feasible and offers an opportunity in Australia to investigate pregnancy outcomes in relation to the safe use of prescribed medicines in pregnancy.

Funded by an Australian Postgraduate Award.

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 (transition). It was originally funded by a Seeding Grant received from ARACY supporting a new collaboration on this topic. As a result of this collaboration, researchers, families, service providers and policy makers in the areas of education and training, disability, therapy, recreation and employment attended a two day workshop which resulted in the collaborative agreement to produce a research grant application addressing key issues related to the topic of transition.

This grant application, which was successfully funded for 5 years by ARC will commence in 2009. It aims 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 through participation, wellbeing and quality of life. The International Classification of Functioning, Disability and Health (ICF) will be used as a framework. This study is a national collaboration of a broad range of stakeholders including researchers and industry partners representing health, employment and disability with the aim to explore the challenges faced and outcomes achieved by students with an intellectual disability as they move from secondary school into adult life.

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

Rett Syndrome

Describing gross motor abilities, hand function and hand stereotypies using video data

Dr Jenny Downs , Ami Bebbington, Dr Philippa Carter, Peter Jacoby , Anne-Marie Williams, Professor Walter Kaufmann, Dr Helen Leonard.

Since Rett syndrome is a movement disorder an extremely important and innovative source of study data is video footage provided by the subjects' families. Many families participating in the Australian Rett Syndrome Database have recorded video footage showing their daughters' participation in activities of daily living. We have collected video data in 2004 and more recently in 2007/2008, and some families have submitted a video on two occasions. We have developed validated coding systems for gross motor function, hand function and hand stereotypes. These data have been analysed in relationship to age and genotype, giving a greater understanding of the phenotype of Rett syndrome. Further, we have preliminary evidence to support the validity of the measures that we developed to assess gross motor and hand function and these tools that are specific to Rett syndrome could be useful as measures in future clinical trials.

Our next task is to analyse longitudinal changes in the domains of gross motor and hand function.

Funded by the NHMRC.

International: InterRett

Dr Helen Leonard, Alison Anderson, Professor Nick de Klerk, Professor Sue Fyfe, Professor David Ravine, Dr Le Jian Ami Bebbington, Meg McHugh, Dr Philippa Carter

2008 was a very successful year for the ongoing InterRett project with the number of cases in the database increasing by ~20%. Cases are mainly ascertained through a registration form on our website. Families who register are sent an information sheet and consent form and login details for our online family questionnaire. On completion of the questionnaire we contact one of the attending clinicians and request that they complete the clinician version of our questionnaire. Contributions have been made from 40 different countries with the majority coming from Australia (21%), USA (18%) and France (13%). Translation of the questionnaires into Spanish, French, German, Italian and Mandarin has assisted non-English speaking families to participate. Data from this cohort has contributed to several publications the outputs of which were presented at the Rett Syndrome World Congress in Paris in October 2008. InterRett was also showcased at the conference as a model for data collection for rare disorder

research.

Funded by the International Rett Syndrome Foundation.

Developing clinical guidelines for the management of scoliosis in patients with Rett syndrome

Dr Jenny Downs , Ami Bebbington, Dr Philippa Carter, Dr Helen Leonard, Anke Bergmann, Alison Anderson, Dr Greta Palmer, Professor David Roye, Dr Harold van Bosse, Dr Eva-Lena Larsson, Dr Brian Smith , Dr Gordon Baikie, Professor Sue Fyfe

Scoliosis is a common orthopaedic complication that develops in approximately 75% of girls with Rett syndrome by 13 years of age. There is a limited literature of management strategies for scoliosis in Rett syndrome and it has been difficult to accumulate clinical experience.

We have developed Clinical Guidelines for the management of scoliosis in Rett syndrome based on a systematic review of the literature, the perspectives of parents, and consultation with a multi-disciplinary expert panel of clinicians using a modified Delphi technique. This has followed a life-span approach and includes comprehensive management techniques relevant to physicians, surgeons and allied health professionals. Specific features of Rett syndrome such as genotype, seizures, gastrointestinal disturbances and osteoporosis have been taken into account. The project methdology and a summary of the guidelines has been submitted for publication.

Our next task is to disseminate the guidelines both within Australia and internationally, and we will also assess their reach within the Australian clinical and parent community. We have also collected parent-reported stories concerning the management of scoliosis in their daughter and are currently compiling these perspectives into a booklet to accompany the guidelines document.

Funded by the NIH, International Rett Syndrome Foundation, NHMRC

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

Dr Helen Leonard, Professor Carol Bower, Professor Nick de Klerk, Professor Sue Fyfe, Professor David Ravine, Professor Sven Silburn, Professor John Christodoulou Dr Carolyn Ellaway, Professor Michael Msall, Dr Lakshmi Nagarajan Professor Sheena Reilly , Dr Helen Woodhead , Dr Jenny Downs, Dr Philippa Carter, Carol Philippe, Ami Bebbington, Amanda Jefferson.

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 to three 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.

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.

Progress continues with analytical investigations using data relating to different aspects of the study and during 2008 several articles relating to the study were published. These related to the overlap between autism and Rett syndrome, early determinants of fractures and also to other relationships between clinical features and genotype. Other work undertaken during 2008 involved an evaluation of the impact of scoliosis surgery on activities of daily living, an investigation of the pattern of health service use in Rett syndrome, assessing the impact of polymorphisms in the BDNF gene on clinical severity and comparing recent survival in Rett syndrome with that of the series of Austrian cases originally described by Professor Andreas Rett.

Funded by the NIH, NHMRC

Australian-China Alliance: Investigating the relationship between genotype and phenotype in Rett syndrome

Dr Helen Leonard, Alison Anderson, Professor Sue Fyfe, Professor David Ravine, Dr Le Jian

Following our 2007 visit to Beijing our

collaborative work continued with a return visit to the Institute in August 2008 by Professors Bao and Wu from the Peking University First Hospital. This visit allowed us to showcase our data collection methods and our InterRett database which now contains over 50 Chinese cases. Dr Wu gave a presentation on Rett syndrome in China at the Institute and also at Princess Margaret Hospital where we held discussions in regards to clinical management. Our visitors also met with Professor David Ravine to exchange genetic testing techniques. A major achievement from this visit was the drafting of an Australian Leadership Award Fellowship which was successfully obtained. As a result, Dr Bao will be joining us once again at the Institute to focus on data analysis and to contribute to manuscripts between March and April 2009.

Remaining funds from our original travel grant will allow several of our team to return to China to collect clinical data towards the end of 2009.

Funded by DEST Australia-China Fund (Department of Education, Science and Training)

CDKL5

Dr Helen Leonard, Professor John Christodoulou, Dr Meredith Wilson, Alison Anderson, Dr Philippa Carter, Ami Bebbington.

Rett syndrome is associated with a genetic mutation in the ***MECP2*** gene. However, a small group of children in the Rett syndrome population have a genetic abnormality not in ***MECP2*** but in the ***CDKL5*** gene. It is hypothesised that these children have a characteristic gestalt as well as some different clinical features. We have therefore, undertaken collection of photographs to supplement the clinical and family data already obtained through our InterRett project, to investigate the hypothesis. This work is being carried out in collaboration with Professor John Christodoulou and clinical geneticist and dysmorphologist Dr Meredith Wilson both from the Children's Hospital at Westmead in Sydney.

Funded by the International Rett Syndrome Foundation

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

Dr Helen Leonard, Alison Anderson, Professor Nick de Klerk, Dr Liz Milne, Dr Lin Fritschi , Meg McHugh

During 2008 data collection for this pilot study was completed. The main objective of the study was to trial on 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. Two hundred and twenty five parents, who were already participants in the InterRett project, took part. The data collection process was found to be successful from both a participant and research perspective. A manuscript discussing the outcomes is planned for 2009. The pilot simultaneously collected data about the impact of having a child with Rett syndrome on the work practices of parents. This data will be analysed in conjunction with other variables from the InterRett dataset for a second manuscript.

Funded by UWA

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

Professor Carol Bower, Dr Helen Leonard, Jenny Bourke, Professor Nick de Klerk, Professor Sven Silburn, Professor Sue Fyfe, Professor Michael Msall, Paula Dyke, Peter Jacoby, Professor Dennis Hogan, Alana Maley

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 report, published in October 2007, translated the information collected through the Down syndrome NOW study from over 350 families throughout WA with a child with Down syndrome. The report, funded by a grant from the Disability Services Commission, included 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. In 2008 the report was circulated widely to families and other stakeholders.

Further analysis of the data is investigating the economic costs associated with having a child with Down syndrome. A collaboration with US researchers has investigated the individual characteristics, social and demographic factors and types of family functioning which facilitate a pathway to paid employment in young people with Down syndrome aged 17 years and over. The level of individual ability is quite variable amongst young people with Down syndrome and this study showed that greater levels of independence with self-care and mobility were related to higher levels of employment.

Funded by the Disability Services Commission

Capacity Building in Population and Indigenous Health

Community Participation in Population Health research

Anne McKenzie

The Division of Population Sciences continues to have wide-spread support for enhancing and increasing opportunities for greater consumer and community participation its research activities. During 2008 this included:

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

2) Areas such as the Growth and Development Study and the Developmental Pathways in WA Children Project explored new opportunities for greater involvement by the community in their activities.

47 staff and consumers from the Division attending the inaugural ***Involving People in Research Symposium.*** There were 22 presentations on the Division's research projects made to an audience of local, national and international researchers, health professionals and consumers.

An increased number of people seeking input on consumer and community participation from the Consumer and Community Advisory Council or the Consumer Research Liaison Offer during the grant application periods.

Senior staff attending the Community and Community Advisory Council regularly to discuss and seek input on a range of Divisional issues and activities.

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

Increased collaborations and networking opportunities between the Division and the wider community.

The year finished with two researchers from Population Sciences, Jan Payne and Heather D'Antione receiving Health Consumers' Council of WA Excellence Awards for their commitment to consumer and community participation in the Alcohol and Pregnancy Project.

The Division of Population Sciences has continued to show innovative enthusiasm for greater involvement of consumers and the community in all of its activities. As consumer and community participation in research continues to be of interest in the national and international arena, the Division is well placed to continue building its strong leadership position in this area.

Funded by TICHR and UWA

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

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, Wilkes ET, Wright M, Shane Venables.; Coordinator: M Walsh.

In collaboration with Curtin University (the grant holder), Combined Universities Centre for Rural Health, University of Western Australia

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

1. To build capacity of Indigenous Health researchers
2. To improve quality of relevant research, increase Indigenous people's participation in research and identify optimal ways of providing feedback of research findings.
3. To undertake health services research and develop a better understanding of the best and most cost-effective ways of providing preventive and acute care for Indigenous Australians.
4. To investigate lifestyle, behaviours and susceptibility to disease
5. To investigate factors in people's lives that influence health in a positive way- pathways to resilience and wellbeing.

The highlights of 2008 are:

1. M Wright 'submission of PhD thesis.
2. Appointment of N Brown as Director of the Poche Centre for Indigenous Health at University of Sydney
3. Award of NHMRC postdoctoral fellowships to M Wright and C Kickett-Tucker,
4. Award of 6 NHMRC/ARC grants
5. Jan Hammill becoming a Member (AM) in the General Division for service to the community through health services for Indigenous women and children and research into the effects of foetal alcohol syndrome.

To date team investigators have had 24 publications in peer-reviewed journals and published 3 book chapters.

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

The ICBG 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,

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, Smibert 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 are now analysing the data collected in the 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. 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 and 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. Follow-up telephone interviews asked about occupational and other exposures. Blood and buccal samples were taken from the case child (in remission), and blood samples were taken from his/her parents. 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%) consented to take part. 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). Analysis of the final datasets is well under way. Initial analyses should be complete by mid 2009.

Funded by the 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, dalla Pozza L, Daubenton J

The Australian Study of Childhood Brain Tumours (AUS-CBT) is a national, NHMRC funded, case-control study into the causes of childhood brain tumours (CBT). It aims to investigate genetic, dietary and environmental risk factors for CBT, and is the sister study to the Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (AUS-ALL). Researchers in the Childhood Cancer Epidemiology program have now completed three years of the five-year study.

Cases are children aged 0-14 diagnosed with a CBT at one of the nine 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, 378 eligible cases from 2005-2008 have been notified to us. Of these, 288 (76.2%) eligible cases were invited to participate and 197 (52.1%) consented; only 66 (22.9%) families declined to participate. 43 (12.2%) cases will not be invited by the treating oncologist for medical or psychosocial reasons. We are liaising with the clinicians regarding the invitation of the remaining eligible cases and obtaining consent from the families already invited.

Controls are children aged 0-14 who have not been diagnosed with a CBT, and their parents. They are identified using Australia-wide 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 four waves have been completed to date. So far, 422 families have agreed to participate when contacted by phone, and 236 (55.9%) of these families have given their written consent.

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 interviews ask about occupational and other exposures, and DNA (blood or saliva) samples are being collected from the child and parents for genotype analysis. To date, we have received 385 completed exposure questionnaires, 311 food frequency questionnaires and 314 telephone interviews have been completed. 320 families have provided DNA samples and 762 samples have been sent for genotyping.

We continue to work closely with the clinical teams around Australia to ensure complete and timely case ascertainment and consent. We also continue to aim for the highest possible participation and response fractions in completing the data and DNA collection stages of the study.

Funded by the NHMRC

Nutrition and Genome Health in Children: A pilot study

Milne E, Fenech M, Armstrong B, de Klerk NH, Miller M.

The aim of this pilot study was to inform the methods to be used in a larger, NHMRC-funded study of children's diet and DNA damage, commencing in 2009. The specific objectives of the pilot study were:

1. To calibrate a Food Frequency Questionnaire (FFQ) with Dietary Records (DR) for specific nutrient intakes. The calibrations established will be used to estimate children's dietary intake of key nutrients (folate, Vit B12, B6, carotenoids (including retinol), calcium, selenium, magnesium, zinc) and to assist in determining which is the preferred method of dietary data collection.

2. To correlate DNA damage in children with levels of micronutrients in their blood.

3. To determine the success (participation fractions) of different methods of recruiting parents of young children to this study.

We recruited 75 children and their mothers to the pilot study. Mothers were asked to complete the FFQs and DRs about their child's diet several times over a 4 month period, and to give consent for their child to have a small blood sample taken. The blood sample was used to assess the level of nutrients in the blood, and to measure various markers of DNA damage.

Results: The most successful methods of subject recruitment were through schools and playgroups. The laboratory analyses of micronutrients and DNA damage, and the comparison of FFQs and DRs, are currently under way. Results should be available by mid-2009.

Funded by The Cancer Council WA and The Cancer Council NSW

International Case-Control Study into the causes of Embryonal Tumours

Milne E, Armstrong B

The International Study of Embryonal Tumours (ISET) is an international pilot study taking place in 15 countries around the world. The aim of the study is to identify parental and perinatal exposures that may be risk factors for the development of embryonal tumours.

The pilot study is focusing on two types of embryonal tumour, Neuroblastoma and Wilms' Tumour, while the main study would involve all forms non-central nervous system embryonal tumours. The Australian arm of the pilot study is managed from TICHR.

Cases are children aged 0-14 years who were diagnosed in 2008 with either Neuroblastoma or Wilm's tumour at one of the nine paediatric oncology centres around Australia, and their parents. Cases diagnosed during 2007 at Princess Margaret Hospital were also retrospectively recruited. We were notified of 82 cases, 77 (94%) of whom were eligible to participate. Of the eligible case families 65 (84%) have been invited to participate so far, 46 (60%) have consented and 8 families (10%) have declined to be involved. The outstanding invitations and consents will be followed up with the clinical staff in early 2009. Controls are children aged 0-14 years and their parents who were recruited by mail-outs via the Electoral Roll, Medicare and the Midwives Notification System of WA. 82 Control families consented to participate.

Both case and control families are interviewed by telephone about a number of topics including their health prior to conception of the child and during the pregnancy, and their medication, alcohol, tobacco and drug use during this period. Parents are also asked about the medical history of their families, their occupation and whether or not they have been regularly exposed to pesticides at any time in the past. Mothers are also interviewed about the health of their child with the focus on their first 12 months, their vaccination history and any illnesses or allergies they have experienced. DNA saliva samples have been collected by post from a subset of control families as a trial and will be processed to determine the quality and quantity of DNA obtained. All families are being asked whether or not they would be willing to be contacted again if the main international case-control study goes ahead. Australia is the first country to get the ISET pilot phase underway.

Funded by a bequest from the late John Lillie and Bellberry Limited

Growth and Development

Developing evidence-based recommendations for managing childhood obesity

Susan Byrne, Elizabeth Davis, Elizabeth Geelhoed, Eve Blair, Stephen Zubrick.

This study aims to identify the factors that contribute to the development and persistence of overweight and obesity in children, as well as the factors

that lead from overweight and obesity to the development of medical and psychosocial complications. Through the identification of such factors as well as a cost-analysis of the burden of overweight and obesity in children and a focus on the community aspects of childhood obesity we will be able to develop targeted, cost-effective and acceptable prevention and intervention strategies. Ultimately, this will allow effective strategies to be chosen for a particular set of circumstances, rather than applying blanket prevention and intervention strategies that may not be successful and would use unnecessary resources.

Funded by Healthway

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

Dr Katie Suriano, Dr Susan Byrne, Dr Elizabeth Davis

A project within the Childhood Growth and Development Study, this research will investigate the influence of cardio respiratory fitness and adiposity on cardiovascular co-morbidities in children.

Funded by the National Heart Foundation

Cerebral Palsy Research

WA Cerebral Palsy Register

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, carry out research to investigate its causes and evaluate treatment strategies, identify CP as a long-term outcome in other WA studies and assist in the planning of services for people with CP.

The WA Register now also contributes data to the Australian CP Register (ACPR) which was set up to provide information about CP throughout Australia as well as a larger study population to enable more effective research. This was co-ordinated by the WA CP Studies team from its inception in 2002 until 2007 when the administrative centre moved to the CP Institute in NSW where it continues to flourish.

The development of an innovative system to standardise the recording of clinical features of cerebral palsy for the ACPR has been underway for a number of years. Sarah Love and Noula Gibson, who have led this work, devised the Australian Spasticity Assessment Scale (ASAS) and integrated it into a diagrammatic limb-by-limb coding system. This is currently being trialled in a number of States, and train-the-trainer sessions are being planned throughout Australia.

The WA Cerebral Palsy Register was funded by NHMRC Program Grant #353514 (2005-2009). PLAN Australia has generously funded the development of the ASAS and CP Description Form, a PMH Foundation Special Project Grant 2007 has enabled travel to conduct training sessions throughout WA and an Innovative Research Grant from the CP Institute is funding the extension of training across Australia.

Case Control Studies of CP in term and pre-term infants in WA, 1980 to 1995

de Groot J, Blair E, Taylor C, Watson L, Stanley F.

The primary aim of these studies is to prevent the occurrence of brain damage responsible for CP in Western Australia by identifying points on each causal pathway to CP at which it may most effectively, efficiently and ethically be interrupted. Data analysis continues with the intent to explore causal pathways and report research findings at international forums. A/Prof Eve Blair presented findings from the study regarding pre-eclampsia and CP at a conference in Bled, Slovenia, and Kate Taylor has published and presented at a European conference in Turkey on the topic of vanishing twins and CP, a study which quantifies the contribution to CP of co-fetal deaths at or after 20 weeks gestation and co-fetal losses before 20 weeks gestation. Jan de Groot currently has two papers in preparation, one describing study methodology using the example of pre-eclampsia and CP, and the other looking at trends in severity measures for CP cases who graduated from neonatal intensive care. She presented the latter work at the International CP Conference in Sydney where she won the prize for best oral presentation from an emerging new researcher.

Funded by the CP Foundation (2006-08); NHMRC Program Grant (2005-09)

Developmental Pathways in WA Children Project

Stanley, F., de Klerk, N., Bower, C., Li, J., Ferrante, A., Leonard, H., Smith, M., Mathews, R., McKee, M., Barron, L., Marshall, A., Caudwell, V., 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, the Department for Communities, and WA Police. 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 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.

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 A/Prof 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, A/Prof Helen Leonard, Dr 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 uses longitudinal, administrative data from the Western Australian Government Departments of Health and Child Protection to examine the socioeconomic inequalities in child health and development in Western Australia over the past two decades. It is anticipated these findings will establish whether inequalities are increasing between socio-economic groups, as well as between Aboriginal and non-aboriginal children. The findings will also help determine which child, family, and area level indicators contribute to those 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 and Geraldton Regions

Conducted by Glenn Pearson (PhD Candidate), Supervised by Associate Professor Jane Freemantle, Associate Professor David Vicary and Professor 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 in Aboriginal and Torres Strait Islander children: 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.

Developmental Pathways to Mental Health Problems, Suicidal Behaviour and Suicide for Western Australian Youth

Conducted by Kristine Northey.

Supervised by Dr Jianghong Li, Prof Sven Silburn, A/Prof Kate Taylor, A/Prof David Lawrence.

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.

Linking population data sources to better define antenatal, postnatal and environmental risk factors including educational, criminal and antisocial behaviours and health outcomes of children and young adults who have been prescribed stimulant medication for Attention Deficit Disorder in Western Australia

Conducted by Dr Desiree Silva (PhD Candidate), Supervised by A/Prof Carol Bower, Prof Fiona Stanley.

This project aims to investigate the epidemiology and antenatal, intrapartum and postnatal risk factors which are prevalent in children diagnosed and prescribed stimulant medication in WA. It will also investigate outcomes of children on stimulant medication in terms of hospital morbidity, emergency department presentations, mortality (which would include suicide, MVA), literacy and numeracy outcomes, and encounters with the juvenile justice system. The project will consider and describe these findings in relation to possible causal pathways for Attention Deficit Disorder (ADHD), as well as investigate the long and short term effects of stimulant medication in relation to hospital morbidity, mortality and emergency visits, including adverse events.

Database research

IDEA - Intellectual disability exploring answers

Professor Carol Bower, Dr Helen Leonard, Jenny Bourke

IDEA Advisory Council 2008: Dr Bev. Petterson (Chair), Jenny Bourke, Professor Carol Bower, Dr Helen Leonard (TICHR), Dr Simon Williams (PMH), Dr Vera Morgan (UWA), Richard. Sanders (Dept of Education and Training), Dr Anne Mathews (DSC), Kerry. Stopher (DSC),N Cantatore (DSC), Dr Peter Chauvel (Paediatrician), Dr Peter Rowe (SCDC), Charlie Rook (Consumer).

The IDEA Database provides an infrastructure for population-based epidemiological and genetic research into the causes and prevention of intellectual disability. Information in the database is based on data from the Disability Services Commission since 1953, as well as information from the Department of Education for births since 1983. In 2008, IDEA has been updated with notifications of children identified with an intellectual disability from the Department of Education and Training and the Disability Services Commission to the end of 2006. These records are linked by the Western Australian Data Linkage Unit to each other and to all current notifications on the database, in order to minimise any duplications.

Further improvement of records currently in the database has occurred through use of de-identified medical information manually entered from forms from the DSC.

Studies receiving de-identified linked information from the database in 2008 include a study measuring the burden of genetic disease in the WA population and Towards Prevention – A population health approach to child abuse and neglect.

Tabular data were also provided for use

in a study investigating accommodation support for Western Australians with intellectual disability.

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 the 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 Heath 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 2006. 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.

Funded by the NHMRC Program Grant

Western Australian Mortality Database for infants, children and young people: 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, Alpers K, Woods M, Cosgrove P, Anderson IP (University of Melbourne), Stanley FJ.

Work has continued on the database with data now finalised 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.

On of the main aims of the continuing development of this database is the ability to provide comprehensive information that will enable development of targeted policy and evidence based initiatives that will prevent deaths among WA 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. Work has continued on identifying a process and funding source to support the continuation of the collection classification and analysis of these data.

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 the Department for Child Protection

The Western Australian Twin Register

Janice Hansen, Phyllis Alessandri, Nick de Klerk, Michelle 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 and 1979 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, the Molecular Genetics of ADHD, and the relationship between immune functions and asthma and allergy.

Funded by the NHMRC Australian Twin Registry Enabling Grant

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 MZ and 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.

Funded by the NHMRC Australian Twin Registry Enabling Grant

WA Family Connections Genealogical Database

Emma Glasson, Nick de Klerk

The aim of the Western Australian (WA) Family Connections Genealogical project is to create a system of links representing genealogical relationships for the WA population to be used as a research tool in conjunction with health data to help study the inheritance of disease. It is supplementary to the WA Data Linkage System that coordinates regular linkages of records across several population-based health-related data sets. The genealogical links are made using information from birth, death and marriage registrations.

Phase 1 of the project has involved creating genealogical links from information recorded on electronic birth registrations that are available since 1974 and electronic death and marriage registrations available since 1984, totalling approximately 1.3 million records.

Phase 2 will entail encoding genealogical links from earlier paper-based birth, death and marriage registrations, with an initial focus on the 0.9 million records available since 1950. Currently, the genealogy may support genetic and environmental epidemiological research projects for up to three-generational pedigrees. Ultimately, the data may be used to assess the degree of relatedness of individuals within study samples, assist in locating common ancestors and allow estimates of genetic risk.

Examples of projects that have used genealogical data include: health indicators of children born to parents with mental illness, calculation of cancer risks based on population pedigree disease patterns, estimation of the burden of genetic disease in the WA population, socio-economic inequalities in child health, and familial risk factors for the development of diabetic retinopathy.

Dr Glasson was funded 2003-2007 by NHMRC Capacity Building Grant in Population Health Research (#254545), jointly awarded to the Telethon Institute for Child Health Research and UWA School of Population Health. Additional project funding during this time was received by the WA Department of Health. Continuation of funding for 2008 was from the Data Linkage Australia Centre of Excellence awarded to The University of Western Australia.

Autism Spectrum Disorders Research

WA Register for Autism Spectrum Disorders

Emma Glasson, Sarah MacDermott, Glenys Dixon, 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 2200 children, adolescents and some adults who were newly diagnosed with an autism spectrum disorder. After ten years of operation, the data are being used to calculate diagnostic prevalence rates for the WA population.

Funded by the Western Australian Department of Health

International trends in diagnoses and incidence of autism spectrum disorders

Dixon G, Bower C, Leonard H, de Klerk N, Glasson E, Nassar N, Thorsen P, Parner E, Schendel.

This project involves Western Australia, Denmark and the USA. It a unique international collaboration to report on the international trends in diagnoses and incidence of autism spectrum disorders. The observed and widely reported significant increase in Autism Spectrum Disorders (ASDs) has major implications for health service providers, educational institutions and families. There is currently no strong data available on the increase in ASDs. Although there have been numerous studies on the increased prevalence of autism and the apparent 'epidemic' it is still not clear that the increased prevalence is due to a true increase in Autism Spectrum Disorders. Factors such as increased awareness of parents and clinicians; changing diagnostic criteria; methods of reporting and case ascertainment may be accounting for this apparent increase. Some studies have also suggested that there could be a shift in diagnostic categories (e.g. from intellectual disability to ASD). Registers that are population based on geographically defined locations which record year of birth and diagnosis, specific diagnostic categories, use diagnostic criteria that remain constant over time and can control for migration have the capacity to provide the best possible estimate of reliable trends in incidence and prevalence. Both Western Australia and Denmark have registers that fulfil these criteria. This work would be a first in terms of international collaboration in autism research and has come about from funding through Autism Speaks (USA). The results from this collaboration could provide valuable information on the diagnosis, incidence and prevalence of ASDs and would be

invaluable in informing on the future planning requirements for funding of intervention services for children with an ASD according to their age at diagnosis.

Funded by Autism Speaks (USA)

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 has been investigated but the problem of access to vaccination being highly correlated with access to hospitals makes a meaningful analysis problematic. The analysis is continuing, trying to overcome this problem.

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

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

Deborah Lehmann, Hannah Moore, Judith Willis, Catherine Harrison, Leanne Brown, Leonie Waplington in collaboration with Carolien Giele, Paul van Buynder, Michael Watson (Communicable Disease Control Directorate, WA Department of Health), Tony Keil (Department of Microbiology, Princess Margaret Hospital), Denise Murphy (Public Health Bacteriology Laboratory, Brisbane) and Peter Richmond (School of Paediatrics and Child Health, University of Western Australia) for the VISN Network.

The Vaccine Impact Surveillance Network (VISN) was established in 1996 to collect and analyse information pertaining to vaccine-preventable diseases in WA and to assess the impact of vaccination programs. 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 and meningitis and is responsible for approximately 1.6 million deaths annually. IPD primarily affects young children and the elderly, but in Australia, incidence rates across all age groups are high in the Aboriginal population.

Pneumococcal vaccines are specifically designed to cover the serotypes that are most commonly associated with severe IPD. There are currently two types of pneumococcal vaccine; a 23-valent polysaccharide vaccine (Pneumovax, 23vPPV) and a 7-valent conjugate vaccine (Prevenar, 7vPCV). Since 1986, Pneumovax has been available free of charge to Aboriginal adults aged ≥50 years and those with known risk factors aged 15-49 years. Since 2005, Pneumovax has been fully funded by the Federal Government for the elderly and at risk groups. Prevenar was licensed in Australia in 2001 and made available to Aboriginal and other high-risk children (at ages 2, 4, and 6 months) at no cost. Aboriginal children get a booster of Pneumovax at age 18 months. In January 2005 Prevenar became available to all Australian children at no cost.

Although IPD only became notifiable in 2001, VISN has collected epidemiological and microbiological data on all reported IPD cases since 1996. The Communicable Disease Control Directorate (CDCD) at the WA Department of Health took over monitoring IPD from 2008. Throughout 2008, ICHR activity has therefore involved finalising the 1997-2007 data, presenting results at conferences, and preparing publications.

From April 1, 1996 to December 31, 2007, a total of 1913 episodes of IPD were recorded on the VISN database. There has been a substantial decline in 7vPCV-type IPD across all age groups and hence also in adults who are not eligible for vaccination, suggesting a herd immunity effect. However, despite the decline in IPD cases caused by 7vPCV serotypes, there is now a significant increase in IPD due to non-7vPCV serotypes. In particular, we have seen a rise in the incidence due to the non-Prevenar serotype 19A in the non-Aboriginal population and a doubling of IPD rates due to non-7vPCV serotypes in Aboriginal adults aged 30-49 years. Currently there is no register of immunizations in adults. Such a register is needed to assess the impact of adult vaccination programs.

In 2008, two posters were presented at the 6th International Symposium on Pneumococci & Pneumococcal Diseases held in Iceland. One documented the increase in IPD observed within the young Aboriginal adult population whilst the other focused on the recent increase in IPD rates observed in the non-Aboriginal population from 2004-2007. Trends in IPD 1997-2007 were also presented at the PHAA National Immunisation Conference at the Gold Coast. A manuscript documenting these

results is now in advanced draft form.

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

Monitoring carriage of *Streptococcus pneumoniae* among Aboriginal children and adults in Western Australia

Deborah Lehmann, Anke Bergmann, Ruth Monck in collaboration with Jacinta Bowman, Tom Riley (Division of Microbiology and Infectious Diseases, PathWest Laboratory Medicine WA). Carolien Giele, Michael Watson, Paul van Buynder (Communicable Disease Control Directorate, WA Department of Health), Amanda Leach, Kim Hare (Menzies School of Health Research, Darwin) , Peter Richmond (School of Paediatrics and Child Health, University of Western Australia), Tony Keil (Department of Microbiology, Princess Margaret Hospital) in collaboration with WA Aboriginal Community Controlled Health Organisations and remote Aboriginal communities in WA

Streptococcus pneumoniae (pneumococcus) can cause middle ear infection and invasive pneumococcal disease (IPD) resulting in meningitis, pneumonia and septicaemia (blood poisoning). The Australian Aboriginal population has among the highest reported IPD rates worldwide.

The existence of 90 different types (serotypes) of pneumococci increases the challenge of prevention. A vaccine (Prevenar) covering the 7 most common serotypes and a booster with another vaccine (Pneumovax) covering 23 serotypes is offered to Aboriginal children and Pneumovax is also offered to adults. Cause for concern is that IPD is now primarily due to serotypes not included in the Prevenar vaccine.

Pneumococci are carried in the back of the nose of healthy as well as sick individuals. Surveillance of pneumococcal carriage offers important complementary information to data on IPD since it can quickly provide a large amount of information on serotypes circulating in the population, thereby informing public health programs. It also gives a conservative estimate of antibiotic resistance of invasive pneumococcal strains. This study aims to monitor pneumococcal carriage by collecting 300 nose swabs annually from Aboriginal adults and 300 from Aboriginal children in metropolitan, urban, rural and remote areas of Western Australia. We also collect ear swabs from children with ear discharge. Other study aims include: i) describing the prevalence of URT carriage of other pathogens identified on primary culture; ii) comparing pneumococcal carriage rates in Aboriginal children aged < 2 years in the Kalgoorlie-Boulder region with those documented in 1999-2005; iii) comparing the distribution of pneumococcal serotypes in the URT with those causing IPD in Aboriginal adults and children annually; iv) storing pernasal swabs for detection of viruses by PCR to describe the prevalence of respiratory viruses; and v) investigating viral-bacterial interactions in the URT.

We recruit Aboriginal children and adults attending health services for routine examination, immunisation or illness, regardless of whether they have chronic illness. Between August and December of 2008, we collected 320 nose swabs and 13 ear swabs in Wiluna, Kalgoorlie and Roebourne. Our collaboration with the Menzies School of Health Research has recently been enhanced by the award of a joint NHMRC project grant.

Funded by the 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 the 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 PhD project is to describe the aetiology, burden and causal pathways of acute lower respiratory infections (ALRI) in Aboriginal and non-Aboriginal children from a 10-year birth cohort using population linked data. This large data linkage project involves linkages 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 2008 data were received from the Midwives' Notification System, Birth and Death Register, Hospital Morbidity Database System and the Emergency Department Data Collection. The birth cohort dataset has been formed and consists of 245, 249 singleton live births of which 7.1% are Aboriginal. Episodes of ALRI in hospital from children in the birth cohort have been identified and data cleaning of the emergency department dataset to identify ALRI-related metropolitan emergency department presentations is underway.

Preliminary results from this project indicate that 1 in every 4 Aboriginal children and 1 in every 15 non-Aboriginal children under the age of 9 years are admitted to hospital at least once for ALRI. The most common form of ALRI is bronchiolitis which accounted for 11,988 (45.9%) of all ALRI admissions between 1996 and 2005.

Negotiations with data custodians of laboratory data continued in 2008 and it is anticipated that laboratory data will be extracted and linked during 2009. In late 2008, we were awarded an NHMRC Project Grant (number 572590) centred on this project. The study will provide the essential baseline data on which to identify, recommend and evaluate appropriate preventive measures for ALRI in Aboriginal and non-Aboriginal children in WA.

As preliminary work for this project, de-identified data on specimens collected between 1997 and 2005 that were sent to the Department of Microbiology at Princess Margaret Hospital were extracted to investigate seasonal and temporal trends of respiratory viruses. This work highlighted the differences in seasonality between respiratory syncytial virus (RSV), influenza viruses, adenovirus and parainfluenza virus types 1 and 3 and in particular, differences in seasonality of influenza viruses between Aboriginal and non-Aboriginal children. This work has been accepted for publication and was presented at local and national conferences including the Public Health Association of Australia's 11th National Immunisation Conference.

Funded by the NHMRC Program Grant

Hospitalisation for diarrhoea among Western Australian children

Shane Venables, Deborah Lehmann, Hannah Moore

Diarrhoea is a significant reason for hospitalisation in Australia. This study utilising the total population-based databases from the Maternal and Child Health Research Database is investigating the trends in hospital admissions for diarrhoeal diseases in Western Australian children aged <15 years between 1983 and 2006. One major cause of diarrhoeal disease in children is rotavirus and this virus contributes to approximately 50% of children's admissions to hospital for diarrhoeal disease. A rotavirus vaccine was introduced in 2007. This study will be useful in providing baseline data on hospitalisations for diarrhoeal disease prior to the introduction of the vaccine.

NHMRC Program Grant

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. In 2008 the Infectious Diseases Community Reference Group met on four occasions and has had various discussions regarding current projects within the infectious diseases team. The group consists of 8 community members (3 of whom are Indigenous), representatives from the Western Australian Department of Health and The Meningitis Centre, ICHR's community liaison officer and infectious disease researchers.

Funded by the Meningitis Centre

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), Peter Richmond (School of Paediatrics

and Child Health, University of Western Australia), Amanda Leach (Menzies School of Health Research), David Smith (Division of Microbiology and Infectious Disease, PathWest Laboratory Medicine WA).

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 Papua New Guinean infants at 1-2-3 months of age and to find out whether neonatal immunisation in the first week of life will provide earlier protective antibody responses.

The study is assessing the impact of a 7-valent PCV 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.

Enrolment of all 319 study participants was completed in September 2007. By December 2008 all children had completed follow-up to age 15 months and PCV and 23-valent pneumococcal polysaccharide vaccination (PPV). Reactogenicity to PCV was low, but tended to be a little higher in children vaccinated in early infancy than at birth, probably because of their older age and hence more mature immune system. Analysis of cellular immune responses when children were 3 months old demonstrated that neonatal PCV vaccination primes T cell responses with a polarization towards Th2 with no bystander effects on other T cell responses (accepted for publication in Vaccine in December 2008).

Preliminary findings from measurement of pneumococcal serotype-specific antibodies indicate that neonatal and early infant immunisation is safe and immunogenic and that it may delay onset of a first episode of pneumonia in young children.

Ms Jacinta Francis from the Papua New Guinea Institute of Medical Research has submitted her MSc Thesis in which she reports on the maternal and neonatal immune responses to ***Streptococcus pneumoniae*** and how these responses relate to early pneumococcal carriage in the nasopharynx. She has now completed her 2 year stay and returned to PNG.

The research team presented six posters on this project at the 6th International Symposium on Pneumococci and Pneumococcal Diseases in Iceland.

At this meeting Dr. Anita van den Biggelaar was awarded the Robert Austrian Research Award of USD25,000 for her work in pneumococcal vaccinology.

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. Preliminary results from investigation of associations between genotype and acute lower respiratory infections (ALRIs) suggest that several genetic variants from known immune pathways may play a role in the frequency of ALRIs in children in PNG.

In a small pilot project, multiplex PCR at PathWest Laboratory Medicine WA has been used to identify viruses in the nasopharynx of sick and healthy vaccine trial participants. Influenza viruses, respiratory syncytial virus and adenoviruses were more common during ALRI episodes while coronaviruses and rhinoviruses were more common when children were healthy. We will be examining all nasopharyngeal samples for respiratory viruses.

This study is funded by the NHMRC/Welcome Trust International Collaborative Research Grant Number 303123

The Kalgoorlie Otitis Media Research Project - An investigation into the causal pathways to otitis media in Aboriginal and non-Aboriginal children

Deborah Lehmann, Peter Jacoby, Wenxing Sun, Christine Jeffries- Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane, Ruth Monck, Fiona Stanley in collaboration with Bega Garnbirringu Health Services Aboriginal Corporation, Ngunytju Tjitji Pirni 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.

Several papers have been published in 2008. One paper details the rationale, methods, population characteristics and ethical considerations. We have reported in the Medical Journal of Australia that exposure to environmental tobacco smoke is associated with an increased risk of developing OM. In a further publication we report that measurement of otoacoustic emissions at a young age using a simple tool can identify those Aboriginal children who are at risk of getting OM later on. We have now been awarded a Healthway grant to evaluate a program of promoting good ear health and regular screening of Aboriginal children in the Goldfields from birth in order to have children hearing when they reach school age. We also described an improved pulsed field gel electrophoresis for molecular typing 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. We are preparing a paper that describes the respiratory viruses identified in healthy Aboriginal and non-Aboriginal participants and the simultaneous identification of viruses and bacteria.

We have also found that crowding is associated with increased risk of carrying the pneumococcus, nontypeable ***Haemophilus influenzae*** or ***M. catarrhalis*** in the nasopharynx, which is important since carriage of these bacteria is associated with increased risk of OM. Interestingly, exclusive breastfeeding for the first 6-8 weeks of life protects children from carriage of ***Staphylococcus aureus***.

Finally, independent of environmental factors such as crowding, children who carry pneumococcus, nontypeable ***Haemophilus influenzae*** or ***M. catarrhalis*** in the nasopharynx at 1-2 months of age are at increased risk of getting OM.

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

Overview of Developmental Neuroscience Group

Early life stress related gene-environment interactions underlying brain maturation during adolescence

The developmental neuroscience group aims to study the influence of perinatal stress and other psychosocial and environmental factors on newborn, childhood and adolescence health. We are particularly interested in the influence of these factors on the development of stress adaptiveness, cognition and behaviour.

Our research approach is based on a combination of psychosocial epidemiological data analysis, cognitive testing/imaging and genetic and biological analysis of stress-sensitive neuroendocrine function. This approach enables us to address gene-environmental interactions underlying adverse intrauterine development, and the consequential adverse regulation of stress responsiveness, emotion and behaviour in late adolescence. The analysis of developmental trajectories and changes over time during development in our statistical models may enable us to address the complex***'cause or consequence'*** issue related to specific associations observed in our data.

The research in two different pregnancy cohorts (which represents the normal population in Perth and the Peel region of WA, respectively) will allow us to enhance our understanding of the difference between growing up with either i) resilience or ii) vulnerability to adverse intrauterine events and childhood development. The latter may well lead to compromised health during the adult life course.

The Peel Study

Our children, Our Families, Our Place: Enabling Communities for Child Health and Wellbeing

Prof. A McMurray, Prof. F Stanley, Prof. B Down, Dr. PA Stumbles, Dr.GE Kendall, Prof. BJ Waddell, A/Prof. M Simms, Dr. P Franklin, Dr. JAM van Eekelen, Dr. J Li, Dr. E Mattes.

The research focus of this population study using a newly recruited pregnancy cohort in the Peel Region of Western Australia is driven by the hypothesis that increased maternal psychosocial stress *in pregnancy* evokes chronically enhanced neuroendocrine function, which impact on fetal growth via impaired placental function. In the Peel Child Health Study, from 18 weeks of pregnancy on wards, the team of chief investigators collect complementary data on (i) maternal psychosocial stress during pregnancy, (ii) maternal life style, behaviour and social network, (iii) parental self-efficacy, mental health status and environmental conditions of the family house, (iv) serial ultrasounds, (v) resting stress hormone levels in blood, saliva and urine, (vi) polymorphic variation in specific stress and mental health related genes in parents and newborn, (vii) cord blood and placental function, (viii) childhood neuroendocrine, mental health, cognitive and immunological development. In 2008, recruitment has started and progress has been made in terms of questionnaire data collection and biological sampling, processing and storage.

ARC Linkage funding (2007-2011)

The Raine Study - Social, Economic and Psychological and Cultural Determinants of Health

The Western Australian Pregnancy (Raine) Cohort Study: 16/17 Year follow up

The Raine Study Executive:

Prof Ian Puddey (Chair), Prof Fiona Stanley, Prof Lawrie Beilin, Prof Lou Landau, Prof John Newnham, Prof George Yeoh, Prof Jenifer Blackwell.

Raine Study Secretariat/ management

Scientific Director: Assoc Prof Craig Pennell, Prof Nick De Klerk, Ms Jenny Mountain

Website: www.rainestudy.org.au

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 2,868 Western Australian children born between 1989 and 1991 at King Edward Memorial Hospital in Perth. The cohort families were assessed during pregnancy, at one, two, three, five, eight, ten and fourteen years of age The Raine cohort is one of the largest successful prospective cohorts of pregnancy, childhood and adolescence to be carried out anywhere in the world. The Raine Executive encourages the research community to investigate the enormous potential of this unique cohort and the Raine Study Database.

The Raine Study is currently conducting the sixteen/seventeen 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 their parents provide blood and DNA samples. The main research areas for the sixteen/seventeen 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
- 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. Complex schedules, together with busy parents have made it increasingly challenging to recruit the participant families to the follow-up. However the participants 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 16/17yr follow-up is funded by the NHMRC (Stanley et al) Program Grant Appl ID 353514), and other project grants

Child Nutrition and Development (the Raine Study)

(i) Dietary factors and trajectories of mental health from infancy to adolescence

Dr Wendy Oddy, Dr Gina Ambrosini, Dr Therese O'Sullivan, Monique Robinson, Assoc Prof Garth Kendall, Peter Jacoby, Prof Nick de Klerk, Prof Sven R. Silburn

The Nutrition Group is involved in the examination of nutrition and dietary patterns in the Raine Cohort over the years. The team is investigating the dietary factors affecting mental health morbidity from infancy to adolescence and their associations with cognitive and emotional development. The team is examining the extent to which mental health morbidity may be attributable to specific dietary and nutritional factors and how these might mediate and/or moderate other psychosocial risk factors.

(ii) Dietary patterns and ADHD

Amber Howard, Monique Robinson, Dr Jan Piek, Dr Wendy Oddy

Amber Howard explored dietary patterns in the Raine Study cohort and the association of diet and ADHD in her Masters of Clinical Psychology.

Funding : Australian Rotary Health Research

(iii) A longitudinal study of dietary risk factors for cardiovascular disease (metabolic syndrome) and depression in adolescence

Dr Wendy Oddy, Dr Gina Ambrosini, Prof Sven Silburn, Prof Lawrence Beilin, Dr Trevor Mori, Dr Therese O'Sullivan.

The research team is investigating the association of dietary factors with metabolic and depressive outcomes in a longitudinal model using data from the Raine Study Cohort.

Funding: National Heart Foundation/ Beyond Blue grant

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

Prof Lawrence Beilin, Prof Lyle Palmer, Dr Wendy Oddy, Dr Trevor Mori, Assoc Prof Garth Kendall, Dr Beth Hands, Dr Rae-Chi Huang

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.

NHMRC: Project Grant - 403981

Early life stress, adolescent brain development and risk for adverse cognitive and psychosocial outcomes (the Raine Study)

Dr. Anke van Eekelen, Dr. Eugen Mattes, Assoc Prof. Jonathan Foster

The neuro-cognitive team aim to study pre and postnatal (stress) factors and examine their association with HPA-functioning, cognition, and mental health during childhood and adolescence in the Western Australian Pregnancy Cohort (Raine) Study and the Peel Child Health Study. Intrauterine and childhood exposures include trajectories of stressful life events, family functioning and mental health status but also effects of intrauterine and postnatal growth patterns, and a comprehensive range of psychosocial, familial and environmental factors. This research also aims to include genetics in the biological analysis of stress-sensitive neuroendocrine function by (a) characterising polymorphisms of the participants' glucocorticoid receptor, mineralocorticoid receptor and serotonin transporter genes and (b) examining interactions with early life exposures and their epigenetic and neurobiological consequences. In 2008, we continued collecting (i) data in the field of mental health and cognitive and neuroendocrine development as part of the Raine Study follow up at 16 years of age, and (ii) data on stress responsiveness at the Raine Study stress test at 18 years of age.

Funded by **NHMRC (2007-2009) / Women and Infants Research Foundation of Western Australia (WIRF; 2006-2008)/ Canadian Institutes of Health Research (CIHR; 2007-2010),** ARC/NHMRC Program Support for New Collaborations through ARACY/NGED networks 2008.

Prenatal androgen exposure and its influence on mental health in childhood and adolescence (the Raine Study)

Dr Eugen Mattes, Prof Martha Hickey, Prof Ian McKeague, Prof Ezra Susser

We aim to investigate whether high or low levels of testosterone and other androgens in the circulation of a baby at the end of pregnancy may influence their behaviour and mental health as a child and teenager. The human brain is highly sensitive to testosterone. We propose to use developmental trajectory models to describe the effects of androgen exposure measured in blood from the umbilical cord on complex behavioural patterns over time which underpin adolescent mental health problems and risk taking behaviour. This will be studied in the Western Australian Pregnancy

Cohort (Raine) Study. Our findings have the potential to indicate new pathways of behavioural and disease origin and to indicate critical periods for intervention that may lead to improvements in lifelong health.

Australian Rotary Health Research Fund (2008-2009)

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

Prof Leon Straker, Assoc Prof Peter O'Sullivan, Dr Anne Smith, Dr Andrew Briggs

The Raine Study musculo-skeletal group aim to develop a clearer understanding of the complex development of spinal pain disorders in childhood and adolescence in order to create new, effective and cost-efficient preventive and therapeutic interventions. The team is investigating the complex development of back and neck pain from childhood, through adolescence, into early adulthood. The group are evaluating the contributions of risk factors from physical (posture, fitness, motor competence, body composition), lifestyle (computer and TV use, physical activity, school bag use, diet, drug use) and psychosocial (depression, anxiety, stress, coping, fear of movement, back pain beliefs, carer pain, family function, neighborhood feel, socioecomonic status) domains on the development of spinal pain.

NHMRC: Project Grant 323200

The epidemiology and significance of non alcoholic fatty liver disease (NAFLD) among adolescents (the Raine Study)

Prof John Olynyk, Dr Leon Adams, Dr Oyekoya Ayonrinde.

Non-alcoholic fatty liver disease (NAFLD) is fatty infiltration of the liver which is not related to drinking excess alcohol. NAFLD is related to insulin resistance and the metabolic syndrome. The prevalence of NAFLD in adolescents is unknown. The Raine Study Gastro-intestinal group is determining the prevalence and significance of hepatic and gastroenterological conditions among adolescents. They aim to explore the environmental and genetic modifiers of NAFLD and the metabolic and cardiovascular significance of NAFLD. Raine Study cohort participants undergo a liver ultrasound during their 16/17 follow up assessment.

Funded by the Gastroenterology Society of Australia, UWA

Analysis of stress-induced levels of stress hormone in human blood and saliva of 18 year-old members of the Raine study (the Raine Study)

Dr Anke van Eekelin, Assoc Prof Craig Pennell, Prof John Newnham, Prof Steven Lye, Prof Fiona Stanley

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 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.

CHIR Project Grant

The fetal and early childhood origins of polycystic ovary syndrome. A prospective cohort study (the Raine Study)

Assoc Prof Martha Hickey, Dr Roger Hart, Prof Stephen Franks, Dr Deborah Sloboda, Dr Dorota Doherty

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.

Funded by the NHMRC Project Grant 403968

Genetic epidemiology and the developmental outcomes of health and disease (the Raine Study)

Assoc Prof Craig Pennell, Prof Lyle Palmer, Prof John Newnham, Prof Lawrie Beilin, Prof Fiona Stanley, Dr Anke van Eekelen

Genetic Epidemiology is the study of the determinants of complex human disease and, in particular, the role of genetics in these diseases. The Raine Genetic Epidemiology group is primarily investigating the relationship between antenatal and postnatal environments and how this relationship contributes to the development of adult diseases including metabolic syndrome (coronary heart disease, stroke, insulin resistance, type II diabetes and dyslipidemia),

obesity, neurologic disorders and mental illness. Although adverse antenatal and postnatal environments increase the risk of particular adult diseases, not all individuals exposed to these environments develop these conditions, suggesting that an individuals genotype may contribute to the eventual outcome.

Funded by the NHMRC Project Grant

The Raine Study Dental Health

Dr Linda Slack-Smith, Prof Louise Brealey-Messer, Assoc Prof Garth Kendall.

Dental caries are almost entirely preventable. The Dental Health Research team is looking at the individual factors that contribute to good or bad dental health. They are examining the attendance of families at the school dental services. The research team aim to establish an evidence base to contribute towards the development of health promotion policies directed towards the prevention of dental caries.

Funded by Healthway

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

Dr Eugen Mattes, Prof Sven Silburn, Prof Steve Zubrick, Assoc Prof Garth Kendall, Dr Wendy Oddy, Dr Jianghong Li, Monique Robinson.

The Raine Mental health group is examining the effects of antenatal and childhood risk factors on child and adolescent mental health in the Raine Cohort and this work forms the basis of Monique Robinson's PhD. Information on biological, psychological characteristics of participants in the Raine Study will be used to identify pathways to healthy and adverse mental health outcomes.

Funded by the NH&MRC Program Grant

ARACY & ARC/NHMRC Early Career Researcher Scholarship

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 and International Consortium for the Monitoring of Child Development has been formed between the Offord Centre at McMaster University and the Human Early Learning Partnership in Canada along with the Telethon Institute for Child Health Research and the Centre for Community Child Health in Australia, with the WorldBank as a partner organisation. Currently the Institute for Child Health Research is involved in supporting Indonesia with countries such as China, Bangladesh, Brazil 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 the Department of Education and Training. Department of Health.

Centre for Developmental Health

Silburn S, Zubrick S, D Lawrence, K Taylor.

The Centre for Developmental Health (CDH) is a joint venture between Curtin University of Technology and the Telethon Institute for Child Health Research. CDH aspires to identify and understand the pathway mechanisms that lead to greater social, civic and economic participation of individuals and populations. CDH aims to:

(1) conduct high quality, nationally and internationally recognised research in fields related to developmental health

(2) apply research findings to guide healthy public policy across sectors to improve the health of children, adolescents and families; train the next generation of researchers; and advocate for research and for children's health and wellbeing Strategies to achieve these aims

include:

(1) coordinating and enhancing multidisciplinary research and policy and planning advice in the field of developmental health;

(2) developing national and international links in relevant academic and policy areas of developmental health;

(3) developing links with agencies and facilities impacting developmental health in Western Australia, Australia and internationally; and

(4) assisting staff in related areas to increase their research activity in support of the developmental health and well-being agenda.

2008 Western Australian Child Development Study

Zubrick SR, Lawrence D, Mitrou F, De Maio, J.

This project covers the planning and development phase of the Western Australian Child Development Study, which was planned as a follow-on to the 1993 WA Child Health Survey, and the WA Aboriginal Child Health Survey (WAACHS). The main survey was to be a state-wide representative sample of around 3,000 families including around 5,500 children aged 0-17 years. The broad aims were to describe the overall development and wellbeing of children and young people in WA, and to identify factors associated with both positive and negative outcomes for children and families. The project was unsuccessful in obtaining funding through the state budget, and has now been discontinued.

Questionnaires for both household and schools phases of the study were developed through an extensive consultation process. Using the materials from the 1993 WA CHS and the WAACHS, a thorough review of surveys, questionnaires and instruments from around the world was undertaken. Guided by consultation with the survey steering committee and consumer reference groups the most appropriate materials for the survey were identified, and areas where new questions or instruments were required were agreed on. These were then developed in consultation with a range of experts in each of the relevant subject fields. An initial pilot test was conducted, and questionnaires were converted into electronic format to enable data capture via computer assisted interviewing.

Funded by the Health Department of WA

1993 Western Australian Child Health Survey – 15 years on

Zubrick SR, Silburn SR, Lawrence D, Stanley FJ.

The 1993 WA Child Health Survey (WA CHS) was a ground-breaking large-scale survey of children and families across Western Australia. This study sought to follow what had happened to the survey children in the 15 years since the survey, using record linkage to WA health records including hospital admissions, birth records, and mental health services contacts. A specific focus of the study was to determine if information collected in the 1993 survey could predict subsequent early pregnancies and poor birth outcomes, deliberate self-harm attempts, and contacts with Mental Health Services in WA.

The WA CHS covered physical health, social and emotional wellbeing, family and community health and education. Information was collected from parents and carers, young people aged 12 – 16 years, and from school teachers and principals. At the time it was conducted, the survey was ground-breaking in terms of the breadth and depth of its coverage, and in some areas it remains the primary source of information on Western Australian children and families. The results provided a snapshot in time and were used to inform major policy documents at both state and national level.

Using information from birth, hospital and mental health records, we found a range of factors assessed in the 1993 WA CHS were associated with adverse outcomes for young people. Specific areas where findings have been made include teenage pregnancy and deliberate self-harm.

Funded by the Western Australian Health Promotion Foundation (Healthway)

Restor(y)ing Aboriginal Parenting (TOO SOLID)

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

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)

Funded by the NHMRC: Aboriginal and Torres Strait Islander Research, A Healthy Start To Life

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 Twins and Singletons with Specific Language Impairment (LOOKING at Language) project is funded by the USA National Institutes of Health from 1 July 2002 – 30 June 2012. The LOOKING at Language Study is investigating genetic, neurobiological and environmental risks for Specific Language Impairment and Reading Disorder in twins and singletons from 2-9 years. Specific Language Impairment (SLI) is a disorder where children struggle with language acquisition for no apparent reason. These children do not have a hearing or intellectual problem, they have a specific problem with language. SLI affects approximately seven percent of single-born children with otherwise normal development. The rate of SLI in twins is not known. The project addresses two of the four NIH priority areas for research in communication disorders: (1) Determining factors that contribute to or cause normal and disordered communication and (2) developing and refining diagnostic criteria to facilitate early diagnosis of communication disorders. Following recent progress in the identification of gene linkages for children with speech impairments and likely gene locations for SLI, we will also conduct molecular genetic studies of the families. In 2008, Rice, Taylor and Zubrick published a paper that showed that by seven years of age, 80% of late talkers had caught up, and that boys were at no greater risk for language impairment than girls. However, one in five late talkers was below age expectations for language at school-age. In 2008, Zubrick, Taylor, Rice and Slegers received the American Speech Language Hearing Editor's award for the most outstanding article on language published in the Journal of Speech, Language, and Hearing Research for a paper on the prevalence and predictors of early language delay in two-year-old children.

Funded by the National Institutes of Health

ARACY Evidence in Action Topical Paper

Professor Sven Silburn, Dr Roz Walker.

Community Learning for Parenthood. This Topical paper was commissioned by the Australian Research Alliance for Children and Youth (ARACY) as resource for CfC practitioners, It provides CfC Managers with practical, evidence-based approaches of what works, why it works and strategies that ought to be implemented to improve the services that cater for the well being of young children and their families. This discussion paper encompasses a development framework starting with pre-conception through to 5 years old, an overarching theme is the factors that influence child development with particular attention to developmental influences, understanding foetal programming and the importance of nutrition, on adult health outcomes and wellbeing. A webinar and power point were also presented nationally.

Funded by ARACY

Suicide Prevention

Suicide prevention research and translation project

Silburn S (Chair), Phillips S (Executive Officer), Robertson D, Northey K, Miller K, Adey K, George N.

The Institute's program of translational research in suicide prevention aims to ensure current policy and practice for the prevention of suicide and suicidal behaviour is informed by current scientific knowledge. The Institute also provides a secretariat for the Ministerial Council for Suicide Prevention. The Council is administratively based at the Institute and reports to the Minister for Mental Health. It includes senior representation of all government departments concerned with human ser vices, non-government agencies, carers, consumers and other community stakeholders.

Following the change of government in September 2008, the Ministerial Council for Suicide Prevention presented the incoming Minister for Mental Health with a draft WA State Suicide Prevention Strategy, based on a state wide consultation process, a review of the literature and extensive consultation with key stakeholders and government agencies.

The Ministerial Council for Suicide Prevention is currently in recess, waiting on the Minister for Mental Health to announce a $13Million State Suicide Prevention Strategy and the Council's role in delivering the strategy.

Integrated proactive suicide bereavement postvention project

Silburn, S, English B, Phillips S, Hillman S, Bromley L,.Riseborough P, Staples K, Ugle K, Glassen B.

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.

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.

Funded by the Commonwealth Department of Health and Ageing

The Applied Research Projects in Child Health

ADHD Raine project

Grant Smith, Stephanie Jackiewicz

The current project used the Raine study data to meet three major objectives: 1) to identify early predictors and possible causative factors in the development of ADHD; 2) to examine the effects of stimulant medication on the long-term social, emotional and academic outcomes of children with ADHD, and; 3) examine the long-term physical side-effects associated with stimulant medication in the treatment of ADHD.

Summary of results for each aim

1) A multivariable model examining the independent effects of birth, pregnancy, and early childhood measures on a child later developing ADHD indicated a number of significant predictors: Mother's BMI, stress during pregnancy, post-natal depression, and early introduction of solids.

2) The effects of stimulant medication on a number of social, emotional and educational measures (taken at 13 years of age) of children who had received a diagnosis of ADHD were assessed through a number of general linear models and binary logistic regression models. These analyses indicated no significant relationship between stimulant medication and long-term social, emotional and educational outcomes. However, the non-significant trend for all outcomes measures suggested poorer outcomes for children on medication.

3) The effects of stimulant medication on height, weight, and heart function of children who had been diagnosed with ADHD were examined at 13 years. Height was not found to be associated with medication usage. Weight was significantly associated with medication usage, with children who were currently receiving medication (at 13 years) being significantly lighter than those who had never received medication. Systolic blood pressure was not associated with medication use, however diastolic blood pressure and resting heart rate were: Compared to children who had never received stimulant medication those who were currently receiving stimulant medication had higher diastolic blood pressure and heart rate. Those who had medication in the past (but were not receiving it at age 13) had average values that fell between these two groups (however this was not significantly different to either group). This suggests that there may be an effect of medication on heart function that lasts after medication has ceased. Further research should be conducted to examine the long-term effect of stimulant medication on heart function.

The current study had a number of major limitations that prevent strong conclusions being formed based on the results. However, the results do indicate that a purpose-designed, rigorous study examining the effects of medication on the long-term outcomes of children with ADHD is required.

These results have been assembled in a report and distributed to the members of the Western Australian Ministerial Implementation Committee for ADHD (MICADHD). The plan for dissemination of the findings will be discussed at the next meeting for MICADHD.

Funded by the Western Australian Health Department of WA

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

Roz Walker, Stephanie Jackiewicz

The WA Department of Health (WA DOH) has noted higher rates of psycho stimulant prescription in Western Australia compared with other Australian jurisdictions. In children, prescription for psycho stimulant medication is predominantly associated with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).

A diagnosis of ADHD relates to a pervasive pattern of behavioural and cognitive symptoms with impairing levels of hyperactivity, inattention and impulsiveness. It is one of the most common behavioural disorders among children and its symptoms often persist into adulthood.

Treatment with psycho-stimulants (dexamphetamine and methylphenidate), either alone or in concert with psychosocial therapies, has been shown to be effective and safe in the short term, and has the potential to significantly improve the quality of life of both children with ADHD and their families. However further research is required to

understand the ADHD diagnostic process and pathways to psycho-stimulant treatment in Western Australia, in the context of high prescription rates of this medication compared with available data in other states.

The current project comprises a small qualitative project that aims to identify pathways to diagnosis of ADHD. There has been limited research into the pathways to diagnosis of ADHD. What influences parents to seek help for this symptomatology, where do they seek initial advice, does this advice impact their decision about where to go for help, who influences their decisions? In order to collect this exploratory type of data it is necessary to conduct a qualitative project that will give rich family centred data.

This project will form a compilation of a small number of "case-studies" characterising ADHD pathways to diagnosis and related issues for Western Australian children. These case studies would outline experiences of families and children diagnosed and treated for ADHD.

Themes emerging from these case studies will inform future phases of this larger research project/agenda to be agreed in collaboration with the DOH and specialists. They may include:

A survey of families of children with ADHD to clearly identify the pathways to diagnosis in Western Australia.

An exploration of the decision making and diagnosis pathways implemented by specialists treating ADHD in Western Australia.

A comparative study of Western Australian families decisions regarding the use of ADHD treatments.

A comparative study between states of Australia identifying diagnosis pathways and treatments choices.

We are currently in the field with collecting data from families and are investigating alternative recruitment strategies.

Funded by the Western 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 TICHR 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 was 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 was launched in July 2008.

Funded by the North Metropolitan Area Health Service

Promoting Optimal Infant Nutrition: The Perth Breastfeeding Scoping Project

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

In February 2006, an application was made by the Collaboration, Wendy Oddy and North Metropolitan Area of Perth (NMAHS) to Healthway for a Health Promotion Research Grant. 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 NMAHS, Western Australia. We were awarded this grant and have now completed the research project.

The following is the executive summary from the final report to Healthway [submitted 31 August 2008]

- The aim of "Promoting Optimal Infant Nutrition": The Perth Breastfeeding Scoping Project was to gather information that would allow effective planning of a contextual, multi-level, and collaborative health promotion strategy for breastfeeding in Perth, Western Australia.
- This study aimed to achieve a number of objectives by gathering and synthesising existing evidence

and by conducting focus groups with first time mothers to identify and delve into the issues surrounding initiation and continuation of breastfeeding.

- Globally, a number of breastfeeding interventions have been trialled, ranging from education of mothers on the benefits of breastfeeding to the development of hospital-based interventions.
- The national and international literature is supportive of post natal interventions in improving rates of initiation as well as increasing duration of breastfeeding.
- This study involved two data collection components: the conduct of focus groups with first time mothers of 6-11 month old babies; and an audit of those contexts where women may work and where women go to gain an understanding of how these contexts can either support women to breastfeed or hinder them.
- Focus groups mothers were asked about factors and issues that influenced their breastfeeding. These factors were grouped according to three layers of influence; those that operate at the level of the Individual; Group and Society.
- The results of the focus groups found that the factors associated with breastfeeding success were interdependent. There appears to be an interaction between factors that can hinder a woman's choice to continue breastfeeding – or support her to breastfeed. However, this project could not definitively identify the relative contribution of each of these factors.

The themes at each of the levels included:

1. At the Individual level, mothers reported a series of mother related factors and baby related factors that affected their breastfeeding behaviour. These included physical difficulties to breastfeed, perceptions around lack of milk supply and preparedness for breastfeeding. Child level factors included child being unsettled during breastfeeding, child not responding as expected to being breastfed and the child not requesting the breast.
2. At the Group level, mothers reported a general lack of consistent information from health services such as midwifes and child health nurses to enable first time mothers to know what to expect of their breastfeeding experience. One of the more powerful revelations of the focus groups was that many of these first time mothers were just unprepared for the challenges of breastfeeding.
3. At the Society level, an issue to highlight is that of a mother's perception of society's views of breastfeeding. Many mothers considers society to be supportive of breastfeeding, although this perception was not necessarily seen as a positive reinforcement, particularly for mothers who chose to express breast milk and feed their children by bottle.
4. The results from the audit were inadequate to make any strong conclusions on policy and other practices that may impact on a woman's choice to breastfeed. However, with the limited information available, a number of developing themes were identified with regard to the environments that have the ability to impact upon breastfeeding in WA.
5. It did seem that those places "where mothers go" were supportive of women breastfeeding and valued them as customers. However, whilst support is reported in practice, there was a lack of recognition of the importance of breastfeeding at the formal policy level. Whilst practices within these organisations support breastfeeding "in the now", the lack of formalised breastfeeding policies may allow organisations to easily remove support structures should there be a change in attitudes of the management or changes in management personnel. The recognition of the importance of breastfeeding at a policy level would protect mothers who wish to breastfeed in the future.

The investigators of this study make the following conclusions based on the results:

- Health services require a re-orientation and a commitment to the provision of services that involve consistent information, educational materials and appropriate follow-up (either face to face or over the telephone). The evidence on the effectiveness of behavioural and educational support programs is clear; however, this study still found that information and support provided by midwives, child health nurses and health professionals in Perth Western Australia was still considered to be inadequate to equip first time mothers with the skills and confidence to meet the challenges of breastfeeding.
- Women's perceptions are a powerful force in negatively influencing a woman's breastfeeding experience. Cultural change is more difficult than changing a woman's perception – although programs that focus on

perceptions by first time mothers, in many areas including how hard breastfeeding will be, what others 'think' of breastfeeding and other perceptions of women regarding breastfeeding such as body issues could be implemented and evaluated.

- Social Support from family and friends appears to be a powerful protective factor for women to continue breastfeeding and interventions that address the issue of partner and family influence may have real impact on breastfeeding duration.
- As there is only promising evidence in the national and international literature on multifaceted health promotion programs, a multifaceted intervention on improving breastfeeding duration in mothers living in Perth, Western Australia, that is rigorously evaluated will add considerably to the evidence base in this area.
- Finally, a woman's commitment to breastfeeding, evidenced by a belief that this is the choice that she makes because it is the best for the baby and therefore best for her, combined with her having realistic expectations of the challenges associated with breastfeeding, her having a supportive partner, being prepared for breastfeeding and making a personal decision to breastfeed, rather than a decision made externally could be the most powerful set of factors determining breastfeeding success.

"It's huge but you do it because you want the best for the baby and... you just do it."

We are currently looking at publishing the results of this study.

Funded by the Western Australian Health Promotion Foundation (Healthway)

Asthma Project

Grant Smith

The DOH is currently undertaking a process to develop state-wide clinical guidelines for the management of asthma in children. Information regarding the current state of asthma admission and treatment statewide is required to inform the development of these guidelines.

Specifically, the project examined [1] trends in hospital admissions for asthma in Western Australia [2] regional differences in hospitalisation (length of stay, readmission) for asthma [3] Differences in hospitalisation rates for asthma according to age [4] differences in hospitalisation rates of asthma according to Aboriginality [5] rates of readmission according to hospital and other factors and [6] other areas of interest indicated by the Child and Youth Clinical Network such as the impact of seasonality on hospital admissions for asthma in both metropolitan and regional hospitals.

The results of this project include:

- The vast majority of asthma hospitalisations are diagnosed as "Asthma - Unspecified"
- Hospitalisations for asthma significantly decreased from 2000 to 2003 [we are looking at expanding the analyses to 2006]
- Asthma hospitalisations are more common in winter than the warmer months
- North Metropolitan, South Metropolitan and South West residents have the lowest rates of child hospitalisations for asthma
- Midwest-Murchison and the Great Southern have the highest rates of child hospitalisation for asthma
- Rates of asthma hospitalisations are highest for the following children

1. Under four years of age
2. Male
3. Residing in lower socio-economic areas
4. Aboriginal

- Rates of hospitalisation for Aboriginal children are higher than non-Aboriginal children in all health regions, however the largest discrepancy is within the Great Southern
- Children aged below one year of age seemed to have a lower than expected rate of asthma based on the trends of younger children having a higher rate of hospitalisation

The final report on these analyses is currently being prepared. Negotiation and working in collaboration with clinicians at PMH to interpret the results is an important aspect of the project. The framework for this project has been developed with the view of applying it to other priority health issues for PMH.

Funded by the Western Australian Department of Health

Childhood Injury and Burns Project

Grant Smith, Tanyana Jackiewicz and Rachel Skoss

Injury epidemiology is the foundation to injury prevention strategies.

The challenge for health planners and public health specialists lies in the identification of those families that will benefit the most from injury prevention interventions. The national and international literature has identified some trends in patterns of injury that give us an indication of where prevention efforts should lie. Certain factors, such as

sex and socioeconomic background, affect a child's risk of injury at all developmental stages.

For most types of childhood injury, and for every age after infancy, boys are at a higher risk of injury than girls. Local epidemiological studies have shown that children from low socioeconomic backgrounds and Indigenous Australian children have a higher risk of injury and death from injury than other Australian children. Children from low socioeconomic groups are more likely to suffer injury from certain causes, such as house fire or assault, which are more often fatal than other causes of injury

Further, the likelihood of a child being injured or killed has also been associated with single parenthood, low maternal education, young maternal age at birth, poor housing, large family size, and parental drug or alcohol abuse1. Prevention programs, particularly those that involve home visiting have shown promise in preventing childhood injuries including burns. There is some evidence suggesting that pediatricians, emergency department staff and other clinicians could have a role to play in prevention of burns[2].

There are few studies that use available local Western Australian information that identify a clustering of risk factors that can be used to predict future major burns or head injuries.

This study seeks to explore and better understand the epidemiology of injury, particularly burn and head injury in Western Australia. We want to understand the pre-cursive factors (as far as they relate to contact with the health system) to burn and head injury presentations with the view of developing targeted interventions for those families who may benefit the most from sometimes costly and intensive preventive interventions.

The hypothesis for this research is:

"Children at risk for serious injuries, specifically burns and head injuries can be identified from indicators collected during prior contact with the health system"

The outcomes of this project will be a means of better identifying those 'at-risk' and importantly those who may benefit from preventive interventions, and hence identifying opportunities for 'best bang for the buck" prevention activities.

We are currently refining the data requests for HILB and preparing ethics approval documentation.

Funded by the Western Australian Department of Health

Gestational Diabetes Project

Grant Smith

The major aims of the current study are to identify the impact that gestational diabetes is having on Western Australian mothers and their babies, to indicate how this translates to costs within the health system, and to identify factors that are associated with a higher risk of gestational diabetes.

To meet these broader aims, the following specific research objectives have been identified:

- Describe trends in the incidence of gestational diabetes (GDM) across the whole of WA between the years of 1980 - 2007 and to predict the rates of GDM in the next 10 - 15 years.
- Explore the effect of GDM on a number of suspected negative outcomes during pregnancy, birth, and in the 12 months following the birth for both the infant and the mother.
- Use information gained from the above analyses in conjunction with a literature review to provide a broad indication of the current costs of GDM to the health system and the likely costs over the next 10 - 15 years
- Identify social, demographic, and maternal risk factors (such as obesity) for developing GDM to construct a profile of mothers at greater risk of having gestational diabetes

By meeting the above objectives the study will gain information to aid the WA Department of Health (through the Women's and Newborn's Health Network) in exploring the feasibility of a health promotion or intervention campaign aimed at reducing the levels/ impact of gestational diabetes in Western Australian mothers. It will also provide the Network with information on risk factors that will allow resources to be targeted to those populations most at need.

Significant barriers in the achievement of the above aims have been encountered mainly as a result of issues associated with the integrity of the data. We are currently working around these limitations.

Funded by the Western Australian Department of Health

GIS Injury Project

Kim Clark, Tanyana Jackiewicz.

Concerned at the number of children presenting at Emergency Departments (EDs) with injuries which are preventable, the Trauma, Injury and Poisoning Clinical Network (the Network) approached CARE to develop an injury prevention

strategy. This resulted in the Network commissioning ICHR to establish and trial an injury monitoring system that will use ED presentation data to identify preventable causes of injury and to facilitate the delivery of targeted interventions to prevent further injury events by addressing the underlying cause.

The project is a medium-scale collaborative trial of the use of a geographic information system (GIS) to:

Monitor spatial patterns of injury and related causes using ED presentation data for a defined geographical area [Rockingham/Kwinana] which is the catchment for a metropolitan non-teaching hospital (the Data Collection and Analysis Phase); and

Implement injury prevention strategies to address the underlying cause of clusters of preventable injury that have been identified through the spatial analysis (the Intervention Phase).

The target population will be all children aged between 0 and 14 years, inclusive, who live in the suburbs making up Rockingham and Kwinana and who attend PMH or RKDH EDs or both due to an Injury, Trauma or Poisoning over the study period.

We are currently seeking approval from PMH Ethics to undertake the project and use real time Emergency Department data. Negotiation with PMH and Rockingham/Kwinana District Hospital has taken place and both stakeholders have provided support to the project.

Funded by the Western Australian Department of Health

Aboriginal Consultation Committee for Applied Research and Evaluation

Roz Walker

In mid 2008, CARE appointed an Indigenous Project Lead to establish a steering committee (Aboriginal Consultation Committee for Applied Research and Evaluation; ACCARE) and a project governance structure with Aboriginal representation to ensure the cultural integrity and acceptability of project methodology, program content, implementation evaluation and dissemination of findings of Aboriginal research projects conducted by CARE. ACCARE is a very important part of TICHR's Aboriginal research program.

Funded by the Telethon Institute for Child Health Research

Antenatal Audit Project

Dr Tracy Reibel, Associate Professor Roz Walker.

This project seeks to address some of the short and long-term consequences of lack of access to antenatal care for Indigenous women. The project overall aims to develop an antenatal service delivery model for ATSI women in a geographically defined region of the Perth metropolitan area.

Project Objectives: The study team has:

1. Undertaken an audit of antenatal services for ATSI women in Western Australia;
2. Will be undertaking an impact assessment of current antenatal service models on their target audience(s) by examining key performance indicators such as birth weight for specific catchment areas covered by these service models in one or more geographic areas of Perth metropolitan region.

The assumptions that underpinned the audit tool were that Aboriginal women's birth outcomes are worse than for non-Indigenous women, that models of care that target disadvantaged women are required and that many Aboriginal women have complex care needs during pregnancy.

The findings of the audit of antenatal services are summarised below:

- After a process of elimination, 35 health services or organisations were identified as providing an antenatal service, with 31 health services currently confirmed as providing antenatal care to Aboriginal women.
- Of the 31 services:
    - 11 are specifically for Aboriginal women
    - Of the 20 remaining services, Aboriginal women accounted for:
    - 9 services >50% (range 50-100%)
        - 4 services < 25%
        - 7 services <10%
- There are a range of general characteristics that are confirmed by the audit data.
- First antenatal contact is most likely to occur in the second trimester of pregnancy however a significant amount of first contact occurs in the third trimester of pregnancy. Some services report first contact as occurring with any of a range of health professionals, with the overall spread across the professions similar in number. Services where the client base is more than 50% Aboriginal women appear to have a higher rate of antenatal visits (average 5) for each woman.
- Antenatal services specifically provided for Aboriginal women are more likely to be located in the community and be funded

by the Federal government or a combination of Federal and State funding. Non-specific services are more likely to be hospital based and state funded. The length of time a service has been operating may have an impact on the number of antenatal visits per Aboriginal woman.

- Risk assessment and reduction and education appear to be managed in a reasonably consistent manner across different health services. It was noted that childbirth and parenting education is mostly provided one-to-one, often on an opportunistic basis and that Aboriginal women do not usually access mainstream classes.
- Access and availability of transport to antenatal care across audited services appears to be well managed. Multidisciplinary antenatal care involving Aboriginal Health Workers, Midwives, General Practitioner and/or Obstetricians and Community or Child Health Nurses is consistently available across audited services, although Aboriginal Health Workers were less represented.

In the process of conducting this audit it has become apparent that two other similar exercises are currently being conducted:

1. State Perinatal Committee is mapping all services for Aboriginal people
2. Women's and Newborns Health Network is conducting a survey of antenatal services for Aboriginal women

It would be useful for an overview of various components of these activities is prepared and circulated, identifying the aims and objectives of each project and where there may be overlap and an opportunity to share information.

It is evident that pregnant Aboriginal women are not a homogenous group. Rather there is a diversity of communities, and diversity within communities, and combined with the high degree of mobility of Aboriginal people, these circumstances present unique challenges in providing effective and appropriate antenatal care to all Aboriginal women.

We are currently investigating the feasibility of undertaking an impact assessment. It is likely that we will take these findings to the broader reference group and ask for their advice as to the next steps for this project.

Funded by the Western Australian Department of Health

Improved communication and informed decision making by Aboriginal and Torres Straits Islander families: Prenatal diagnosis, neonatal care, and end of life decisions

Roz Walker

This qualitative research project demonstrates a real commitment to process and inclusive research design for Aboriginal research at TICHR. The project aims to investigate and develop communication and decision making processes between Aboriginal families and health care providers. The project will consult with Aboriginal families and other interested parties on communications issues in relation to decision making in a neonatal setting.

The project has been endorsed by the Aboriginal Consultation Committee for Applied Research and Evaluation (ACCARE) which comprises representatives of key WA Aboriginal health services and agencies. ACCARE provides guidance and direction to all Indigenous research projects within our team. The Aboriginal Health Council of WA (AHCWA) is also assisting with disseminating information and enlisting support for this project.

Due to the sensitive nature of this project, recruitment of participants will be managed very carefully. There are potential difficulties and ethical dilemmas of specifically recruiting Aboriginal women who were previously patients in KEMH/ (or mothers of patients in PMH) and had been required to make decisions around of end of life decisions or transition to palliative care.

To address these challenges of recruitment we are seeking assistance through local networks to provide information about this project to Aboriginal women over 18 years (and their families) from communities in WA who wish to discuss their experiences in communicating within the medical system over critical care issues which may encompass prenatal diagnosis and neonatal care resulting in end of life decisions including the transition to palliative care at some point between 2000 and 2006. This process was applied by the SIDS Foundation when carrying out research of an equally sensitive nature and was highly successful in recruiting people. The majority of participants also commented on the importance and benefits of the research for them

The project team will also enlist the support of Aboriginal health workers, health professionals to talk about the project with Aboriginal community members. Local Aboriginal people will also be engaged as cultural guides and if necessary as interpreters to facilitate ongoing collaboration and discussion in each community to help the project team.

Ethics approval has been provided for this project and we are currently planning data collection protocols and recruitment.

Funded by the Western Australian Department of Health

Evaluating the Halls Creek Mother Support Initiative

Roz Walker, Kate Muggliston, Valma Banks (HCMSI Program Co-ordinator) , Aisla Munns (ABHI, School of Nursing, Curtin University of Technology

This project aims to evaluate the Halls Creek Mother's Support Initiative (HCMSI) –'Yanan Ngurrangu Ngamayiu', which is a community-based maternal and child health prevention and education program for Halls Creek and the immediate surrounding communities. 'Yanan Ngurrangu Ngamayiu' is a home-visiting program for Aboriginal pregnant women and parents of young children 0-3 years old which commenced in 2008.

Experienced Aboriginal mothers and grandmothers are trained as community care workers to provide parents with support to improve the home environment, parental health behaviour and attitudes, and infant and child health outcomes through a range of activities including home visiting. The HCSMI key objectives are to improve: mothers self esteem and self-efficacy; antenatal care and outcomes for pregnant women; increase maternal and child health skills and knowledge and improve the physical, social and emotional wellbeing of their children aged 0-3.

This study will evaluate the HCMSI program using a participatory process to empower staff and participants which involves collecting stories about the most significant changes that occur for parents, children and staff as a result of their involvement with the HCMSI program. The ultimate aim is to identify and strengthen the elements of the program that improve their situation and the achieve the program's primary objectives and address any elements that impact unfavourably on their situation or the program.

Western Australian Department of Health

The ARACY Seeding Grant

Roz Walker, Ernest Stringer Ngaanyatjarra and Sven Silburn.

Facilitating the Warburton Remote Community Consultation Process.
A unique opportunity exists for a collaboration to undertake a three phase planning process to develop a large scale ARC/NHMRC submission that: brings together high level expertise; builds on established relationships and engages community support and participation.

Funding was successfully obtained in November 2008 to support the initial consultation and planning for this initiative. Representatives from Ngaanyatjarra Council, Warburton School, Goldfields District Office and WA Department of Education, WA AETC and the Collaboration for Applied Research and Evaluation at the Telethon Institute for Child Health

Researchers have come together to discuss how the disparity in education, health and wellbeing outcomes experienced at the Warburton and throughout the Ngaanyatjarra lands can be improved. This is a pressing question with important policy and practice implications. This proposal encompasses the broad principles of capacity building, sustainability, knowledge generation and policy translation.

A key aim of the process is to consult with and gather together relevant community stakeholders so they can identify changes needed as a community and have ownership and capacity to do it. The activities planned are designed to build trust among all participants, and to identify and involve all relevant stakeholders throughout the process; and, to enable the Ngaanyatjarra Council to contribute to all phases of the research from its inception to its implementation, communication and dissemination and its monitoring and evaluation and translation to policy.

Expected outcomes of collaboration include:

- An EOI submitted for an ARC Linkage Grant application by March 2009.
- National Webinar – powerpoint presentation outlining the consultation and engagement.
- Increased partners committed to the collaboration.
- A review of literature and summary of the research topic for investigation.

Funded by the ARACY ARC/NHMRC 'Future Generation' Research Network

A follow up study of Best Beginnings clients

Kim Clark, Tanyana Jackiewicz.

Best Beginnings was launched in Western Australia in late 2000, originally as one of a suite of programs that collectively formed the "Building Blocks" initiative – a comprehensive multi-department response to the health and well-being of children during their early years.

Intervention commences ante- or post-natally (up to 3 months following childbirth) and is accessed via professional referral. Referral is voluntary and made on the basis of behavioural, psychosocial and environmental risk factors for poor maternal and child health or well-being. The formal program includes 19 home visits which occur during the first 2 years of birth. Home visits are often supplemented with other forms of contact between PSW's and clients (e.g. phone calls).

Service delivery is supported by case conferencing, which is overseen by Child Health Clinical Nurse Specialists and Child Protection Team Leaders. Child Protection Team Leaders are responsible for supervision of staff and management of the program at the local level. Case conferencing and supervision is considered critical to the integrity of the program.

Our study of former Best Beginnings clients had two components: (1) a telephone survey of former Best Beginnings clients using a structured questionnaire; and (2) in-depth interviews with a sample of 10-12 clients that had been contacted for the telephone survey and were willing to participate in a further face-to-face interview.

We have completed the telephone survey and have produced a report on the findings of this survey. The sample for the telephone survey was attained by attempting to contact former clients who had previously consented to be followed up and could be located. Apparent database errors in the recording of consent to be followed up significantly reduced the potential client group from which a sample could be drawn. Further, given the length of time between their last contact with a Best Beginnings' PSW and the follow up attempt (the median gap was 3+ yrs), locating former clients routinely proved difficult.

The original survey plan entailed sampling 120 Best Beginnings' clients to fill quotas of 20 respondents within 6 categories (20 in each category). The categories related to risk (3 types) and time in the program (2 levels) which had been identified in previous research as relevant to program impact. Unfortunately, difficulties contacting former clients meant that the quotas were not filled and only 96 interviews were completed. Achieving these 96 completed interviews entailed attempting to locate by phone every former Best Beginnings client who met the previously mentioned graduation and engagement criteria and who had agreed to be followed up (n=342). Attempts to contact former clients were only aborted if no current number could be located from the database, white pages listings, from the former PSW or family links or, if there was a current phone number, after the interviewer had made at least 10 unsuccessful attempts to make contact.

Despite the above-mentioned difficulties, the final sample tended to be representative of the 6 client categories identified from earlier research and the participation rate when successful contact was made was very high (86.5%). To deal with any concerns about the representativeness of the sample, the data were weighted to adjust the proportions in each of the 6 categories to their actual levels in the overall client population. Thus, while the final sample in the current study did not match the planned quotas, it does appear to provide a representative sample of former Best Beginnings clients. The median dates of commencement and discharge among the 96 former clients interviewed for this study were 9 April 2004 and 26 December 2005 respectively. Thus, half the sample had been interviewed after a gap of almost 3 years since their last contact with their PSW. The minimum gap between interview and last contact with a PSW was 12 months. Consequently, the responses of former clients to the items in the questionnaire have been provided following substantial opportunity for reflection and experience and are therefore suggested to provide a robust indication of the quality and impact of the program.

These findings also need to be considered with a view to the difficulties faced in evaluating home visiting programs like Best Beginnings. Such programs are tailored to individual client needs and have a range of possible pathways of effect on maternal and child health and wellbeing. Thus, evaluations of home visiting programs confront a "tension between the need for generic outcomes for groups of patients and the desire for individual outcomes reflective of the needs of specific clients".

This study intentionally focused on individual outcomes rather than generic indicators of program effectiveness (e.g. immunisation rates). While some may view this as a weakness, the use of generic outcomes in the short to medium term "misses the point" of a program like Best Beginnings in that the intervention differs quite significantly from person to person. As a consequence, use of generic measures entails the risk of substantially understating the impact of programs like Best Beginnings. Despite the fact that this evaluation has largely focused on individual perceptions of important program impacts, a range of common areas of concern for policy makers in relation to parents of young children have been investigated. These include former clients' assessments of such things as whether Best Beginnings helped them to deal with alcohol and drug problems in their home, its impact on their work situation, and whether it assisted them to return to study.

What then are the messages the responses of former clients in the current study offer Best Beginnings program staff and decision makers in the Departments of Child Protection and Health? In brief, these messages are that most former clients remember the program long after their involvement, they understand what it was trying to achieve, they remain positive about the relationship they had with their PSW, and they believe that the program had both positive short and long term benefits for them and their baby. In other words, in the minds

of former clients, the program worked well for them. Perhaps one of the most telling markers of program effectiveness was that four-in-five former clients (78%) in the current study believed Best Beginnings had a positive impact on ***how well their child grew and developed.*** The degree of apparent success of the program is a testament to the fact that Best Beginnings was derived from an evidence based model, that the lead agency managed the program extremely effectively, that the selection of and support for PSW's has been outstanding; and that the referral and selection processes to recruit clients have been effective.

Where criticisms of Best Beginnings were made by former clients, they largely served to reaffirm the intended program model and indicated that the consequences of a failure to establish a PSW-client relationship consistent with the principles of the Family Partnerships would be that the program benefit would be negligible. Fortunately, the quality control measures built in to Best Beginnings appear to have ensured that few former clients were dissatisfied with their PSW or the program.

Few suggestions for service enhancement can be offered at this stage and it is appropriate to wait until part 2 of this study is completed before any broader reflections are offered. Nonetheless, some aspects of program delivery appear worthy of comment at this point. One is that reducing the scope and frequency of client data collection should proceed to ensure the focus is restricted to information that is of direct relevance to the PSW and to the planning and supervision process. A second aspect of the program that merits comment is the performance of Best Beginnings staff (PSW's) and coordinators. This group of professionals is to be congratulated for their ongoing pursuit of the highest standards of program integrity and their commitment to service improvement; the consequences are plain in the results achieved to date.

We are currently following up clients for in-depth interviews (Part 2 of the study).

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Prudence Thompson BSc(Honours) UWA

Awards

Allen, K. Early Career Investigator Travel Fellowship from the Academy of Eating Disorders and Australian and New Zealand Academy of Eating Disorders. 2008.

Carol Bower, NHMRC Principal Research Fellowship 2005-2009.

Bower, C. Public Health Association of Australia -Fellow of the Public Health Association of Australia (FPHAA), 2008.

D'Antoine, H. Health Consumers' Council (WA) Inc, 2008. Award for excellent Service to Consumers.

France K. Edith Cowan University Excellence Award. Perth.

France K, Payne J. Alcohol Education Research Foundation, Conference Attendance Grant.

France K, Participant, Healthway Leadership Development in Health Promotion Program. 2008-2009.

Gibson, L. Investigating new methods of managing childhood obesity. Healthway Postdoctoral Research Fellowship. 2009-2011.

Hayward, C. Winner, 2008 National NAIDOC Person of the Year;

Hayward, C. Nominee, 2009 Australian of the Year Award;

Hayward, C. National Finalist, Deadlys Awards in the Category of Outstanding Achievement in Aboriginal & Torres Strait Islander Health.

Hayward, C. Recognised in "Western Australia's 50 Most Powerful Women"; Adjunct Professor, Curtin University.

Hayward, C. Recognised in "Who's Who in Western Australia"; Recognised in "Who's Who of Australian Women: Leadership and Beyond".

Hayward, C. Participant, Australia 2020 Summit.

Hayward, C. Chief Investigator on NHMRC approved grant investigating Indigenous Mental Health

Laing, I. The Thoracic Society of Australia and New Zealand /Japanese Respiratory Society Early Career Development Award

laing, I. The Thoracic Society of Australia and New Zealand Peter Phelan Travel Fellowship (Paediatric)

Leonard, H. Circle of Angels Research Award for significant contribution to Rett Syndrome research internationally,International Research Foundation, May 2008.

Leonard, H. Senior Research Fellow, National Health & Medical Research Council, 2009-2013.

Milne, E. NHMRC Career Development Award 2008-2011

Milne, E. High Commendation for the Aileen Plant Medal 2008

Milne, E. Nominated for participation in the Australian Academy of Science High Flyer's Think Tank, Sydney November 2008

Moore, H. Telethon Institute for Child Health Research Postgraduate Student Forum/School of Paediatrics and Child Health Best Presentation Prize, August 2008.

Moore, H. UWA Postgraduate Medical Education and School of Paediatrics and Child Health Student Prize, October 2008.

Oddy, W. Baby Friendly Hospital Initiative Assessor, 2004 – current

Oddy, W. Chairperson, Breastfeeding Public Health Promotion campaign, North Metropolitan Health Service, Western Australia, 2005-present.

Oddy, W. Professional Development Committee, Ngala Family Resource Centre 2009-2010.

O'Leary, C. The University of Western Australia, Graduate Research School Travel Award 2009.

O'Leary, C. Qantas Award Runner-up 2009.

O'Leary, C. Australasian Epidemiology Association 2008 Student Bursary

O'Sullivan, T. Dr Louisa Alessandri Memorial Fund Prize for Scientific Publication. 2008

Payne, J. Finalist, Healthway Awards, 2008: recognizing excellence in Health

Promotion.

Payne, J. Health Consumers' Council (WA) Inc, 2008. Award for excellent Service to Consumers.

Pomat. W. Prize for best paper about research leading to implementation at the 44th Annual Medical Symposium of the Medical Society of Papua New Guinea, September 2008.

Robinson, M. The Stan and Jean Perron Award to Recognise Exceptional Performance by a Research Higher Degree Student in 2008

Robinson, M. Asia-Pacific Academic Consortium for Public Health (APACPH) Early Career Researcher Award: 2008

Robinson, M. Australasian Human Development Association (AHDA) Travel Scholarship: 2008

Robinson, M. Friends of the Institute Award: 2008

Robinson, M. Heart Foundation of Australia Travel Award: 2008

Robinson, M. Grant for Research Student Training Award (UWA): 2008

Zubrick, S. R., Taylor, C. L., Rice, M. L., & Slegers, D. W. 2008 American Speech Language Hearing Editor's award for the most outstanding article on language published in the Journal of Speech, Language, and Hearing Research.

External Committees

State Committees

Gail Barrow, Chair, ARM panel Aboriginal and Intercultural Studies course, Curriculum Council

Gail Barrow, Djidi Djidi Aboriginal Women's Corporation

Eve Blair, 2001- Shaken baby syndrome steering committee, initiated by the WA Child Protection Council

Eve Blair, 2007- Member: scientific advisory sub-committee to the Princess Margaret Hospital for Children Ethics Committee.

Eve Blair, 2008- Chairperson of organising committee for Away Days, ICHR, March 2008

Jenny Bourke, Committee member, Board of Management , Parents of Children with Disabilities (Inc)

Carol Bower, WA Perinatal and Infant Mortality Committee Member 1993-

Carol Bower, Scientific Sub-Committee of the Human Research Ethics Committee, Curtin University of Technology 2000-

Carol Bower, Prenatal Diagnosis Committee, Department of Health WA, 2001-

Ngiare Brown. Co-chair Joint Institutional Aboriginal Ethics Sub-committee of the NT DHCS/Menzies School of Health Research Aboriginal Ethics Sub-committees 2004-

Ngiare Brown.Vice President United Nations Association of Australia, NT branch 2006-

Sue Byrne. Member of Eating Disorder Research Society.

Sue Byrne. Member of the Healthway Health Research Sub-Committee

Sue Byrne. Member of the UWA Vice Chancellor's Postdoctoral Fellowship Committee

Heather D'Antoine. FASD Model of Care Working Group of the WA Child and Youth Health Network, Department of Health, WA. 2008-.

Heather D'Antoine, Chair: WA Aboriginal Health and Information Ethics Committee, Department of Health WA, 2005 –

Heather D'Antoine, Chair: WA Indigenous Sexual Health Advisory Group, Office of Aboriginal Torres Strait Islander Health, 2007 –

Heather D'Antoine, Member: Centre for Aboriginal Studies, Aboriginal Advisory Committee, Curtin University.

Heather D'Antoine, Member: Aboriginal Advisory Committee, Disability Service Commission.

Nick de Klerk, Management Committee, Data Linkage Project, Health Department of WA, 2001-

Nick de Klerk,Executive Committee, Data Linkage Project, Health Department of WA, 2001-

Nick de Klerk,Medical and Scientific Advisory Panel, Cancer Foundation of Western Australia, 2001-

Nick de Klerk, Western Australian Medical Radiation and Cancer Working Party, 2004-

Nick de Klerk, Clinical Drug Trial Committee, Sir Charles Gairdner Hospital, 1986-88, 1990-

Nick de Klerk, Mesothelioma Committee of Western Australia - co-ordinating the Western Australian Mesothelioma Register, 1989-

Nick de Klerk, Busselton Population Medical Research Foundation, Scientific Committee, 1998-

Nick de Klerk, Western Australian Air Quality Co-ordinating Committee Health Issues Group, 1998-

Nick de Klerk, Australian Twin Registry, National Executive

Tracey-Lee Edwards, Member, Asthma Foundation NAPS - Indigenous Women's Project Reference Group

Tracey-Lee Edwards, Member, Central

TAFE Governing Council

Sue Ferguson-Hill, Member, AHCWA Aboriginal Health Promotion Advisory Group

Jonathan Foster – Graylands Ethics Committee (2008)

Colleen Hayward, Chairperson, Selection Panel for WA Citizen of the Year, Indigenous Leadership

Colleen Hayward, Chairperson, Selection Panel for WA Citizen of the Year, Indigenous Youth Scholarship

Colleen Hayward, Member, Celebrate WA Committee

Colleen Hayward, Member, Social Inclusion Reference Group

Colleen Hayward, Ministerial Advisory Council on Child Protection

Colleen Hayward, Leadership WA Board

Colleen Hayward, Member, Selection Panel for Sir Ronald Wilson Leadership Award

Colleen Hayward, Chairperson, Chairperson, Advisory Group on the Prevention and Early Intervention of Family and Domestic Violence

Colleen Hayward, Deputy Chairperson, Ministerial Advisory Council on the Prevention of Deaths of Children and Young People

Colleen Hayward, Member, Directors General Selection Panel Pool of the Commissioner for Public Sector Standards Professor Colleen Hayward, Member, Working with Children Screening Unit panel of Experts

Colleen Hayward, Member, Scitech Aboriginal Education Programs Reference Group

Colleen Hayward, Member, WA State Training Board

Colleen Hayward, Member, National Heart Foundation - WA Board

Colleen Hayward, Deputy Chairperson, WA Constitutional Centre

Colleen Hayward, Member, Selection Panel for Community Services Industry Awards

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

Jocelyn Jones. State Prisoners Review Board

Cheryl Kickett-Tucker. Board member Moorditj Noongar Community College 2005-

Cheryl Kickett-Tucker. Chairperson Koya Aboriginal Corporation 2005-

Cheryl Kickett-Tucker. Member Swan Indigenous Reference Group 2007- and sub-committees Swan Indigenous Womens Group and Governor Stirling Redevelopment Committee

Ingrid Laing. Thoracic Society of Australia and New Zealand (WA) Executive committee 2008-

Ingrid Laing. Asthma Foundation of Western Australia Research Committee October 2007 –

Ingrid Laing. Cystic Fibrosis Association of Western Australia, Mar 1994 –

Deborah Lehmann. Vaccine Impact Surveillance Network Committee, WA, 1998-

Deborah Lehmann. Perinatal and Infant Mortality Committee, Ministry for Health, WA, 2005-

Deborah Lehmann. Princess Margaret Hospital for Children Ethics Committee 2005-

Deborah Lehmann. Meningitis Centre Committee 1998-

Deborah Lehmann. Communicable Disease Control Directorate Strategic Advisory Group 2007-

Deborah Lehmann. Australian Biosecurity Cooperative Research Centre for Emerging Infectious Disease Steering Committee. 2008

Helen Leonard. Executive Committee Perth Epidemiology Group 2008-

Jianghong Li. Health Sciences Faculty Research and Development Committee, Curtin University of Technology

Dr. Eugen Mattes, Dr. Anke van Eekelen: Peel Child helath Study Management Committee (since 2006)

Dr. Eugen Mattes: Western Australian Neurosciences (WANS) Board (since 2007)

Anne McKenzie, Deputy Chair and Board Member, Health Consumers' Council WA Inc.

Anne McKenzie, Member, Health Consumers Council WA Inc.

Anne McKenzie, Consumer Representative, Primary Health Care Research Evaluation & Development Unit Advisory Committee. UWA, Notre Dame University and Combined Universities Centre for Rural Health.

Anne McKenzie, Consumer Representative, Royal Perth Hospital Intensive Care Research.

Anne McKenzie, Consumer Representative, WA Child & Youth Health Network.

Anne McKenzie, Lay Member, Silver Chain Ethics Committee

Elizabeth Milne, Research Committee of Cancer Council of WA (2005-)

Hannah Moore. The Meningitis Centre Management Committee 2008-

Raewyn Mutch. FASD Model of Care Working Group of the WA Child and Youth Health

Network, Department of Health, WA. 2008-.

Colleen O'Leary. FASD Model of Care Working Group of the WA Child and Youth Health Network, Department of Health, WA. 2008-.

Glenn Pearson, Health Department of WA – Child Health and Adolescent Community Health, Aboriginal and Torres Strait Islander Health Reference Group

Glenn Pearson, Public Health Advocacy Institute of WA - Indigenous Smoking Project, Project Advisory Committee

Glenn Pearson, Aboriginal Health Council of WA – Maternal and Child Health Models of Excellence Project, Project Steering Committee

Glenn Pearson, Board Member Health Council of Western Australia Inc

Shawn Phillips, Interagency Implementation and Advisory Group on Suicide Prevention

Dr Clair Scrine, Member, Western Australian Immunisation Alliance

Desiree Silva, WA Neonatal Bed Implementation group

Desiree Silva, 'Womens and Newborns' Health Network

Desiree Silva, HODMAC Joondalup Health Campus

Roz Walker. Working Group, Office of Aboriginal Health, Aboriginal Maternal and Child Care Strategic Planning Advisory Group. (2008–)

Roz Walker. Co-Chair, Women's and Newborns Health Network, Projects Reference Group, Telethon Institute for Child Health Research. (2008–)

Roz Walker. Student Reference Group, Telethon Institute for Child Health Research

Roz Walker. Childcare Links Advisory Group, South Hedland. (2008–)

Roz Walker. Hedland Youth Stakeholder Action Group. Executive Committee, South Hedland. (2007 –)

Roz Walker. Aboriginal Collaboration Council for Applied Research and Evaluation. Telethon Institute for Child Health Research (2008–)

Stephen Zubrick, Member, Curtin University of Technology, School of Public Health, Health Promotion Advisory Committee (1998 - present)

National Committees

Jason Barrow, Mibbinbah Men's Health Program Jason Barrow, CRCAH Link Person

Eve Blair, 2006- National committee for Australasian Academy of Cerebral Palsy and Developmental Medicine.

Eve Blair, 2008- Research committee for Australian Cerebral Palsy Register.

Carol Bower, Australian Birth Defects Society Committee member 1999 –

Carol Bower, Australian Paediatric Surveillance Unit Scientific Review Panel 1998-

Carol Bower, Australian Paediatric Surveillance Unit Board 1998-, Chair (2003-)

Carol Bower, National Child Health Information Advisory Committee (AIHW) 1998-

Carol Bower, National Perinatal Statistics Unit (AIHW) – Australian Congenital Anomalies Monitoring System Advisory Committee

Carol Bower, Intergovernmental Committee on Drugs Working Party on Fetal Alcohol Spectrum Disorder – member 2006-

Carol Bower, Food Standards Australia New Zealand, Folate Fortification Scientific Advisory Group 2006-

Ngiare Brown. Chair NHMRC Indigenous Health Research Panel 2 (Capacity Building) 2006-

Ngiare Brown. Member NHMRC Research Advisory Committee 2007-

Ngiare Brown. Member NHMRC Aboriginal and Torres Strait Islander Health Research Working Committee 2004-

Ngiare Brown. Member Australian Medical Association Indigenous Health Taskforce 2000-

Ngiare Brown. Member Aboriginal and Torres Strait Islander Health Committee, Royal Australasian College of Physicians 2002-

Ngiare Brown. Member Human Rights and Equal Opportunity Commission (HREOC) Health Equality Steering Committee 2006-

Ngiare Brown. Member Human Rights and Equal Opportunity Commission Steering Committee to progress the Right to Health Campaign for Aboriginal and Torres Strait Islander Peoples 2006-

Byrne, S. Member of the The Australian Child and Adolescent Obesity Research Network

Nick de Klerk, Executive Committee, Australian Twin Register, 2001-

Nick de Klerk,Australian NHMRC Asbestos Working Party, 2003-

Nick de Klerk,Australian Working Group developing Radiation Protection Standard for Exposure to ELF, Nick de Klerk,2003-

Tracey-Lee Edwards, Member, The Foundation for Young Australians Board

Sue Ferguson-Hill, Clinical Associate of the New South Wales College of Nursing

Colleen Hayward, Life Member, Aboriginal Education Committee of the Australian Education Union

Tanyana Jackiewicz is a member of the National Community and Child Health Committee

Jocelyn Jones. NHMRC Indigenous Health Research Panel

Jocelyn Jones. Australian Research Alliance for Children and Youth – Network Advisory Committee

Cheryl Kickett-Tucker. Member Future Generations Network, Australian Alliance for Research in Children and Youth 2004-

Cheryl Kickett-Tucker. Member NHMRC Indigenous Health Research Panel 2006-

Cheryl Kickett-Tucker. Member Social and Emotional Health of Aboriginal Children Working Group-Council of Australian Governments 2006-

Deborah Lehmann. Data safety monitoring board for the maternal pneumococcal immunization study in Northern Territory ("PneuMum") 2005-

Deborah Lehmann. GSK Scientific Advisory Panel 2008-

Deborah Lehmann. Australia21 Global Action Plan for the Prevention and Control of Pneumonia Steering Group 2008-

Jianghong Li. Associated Editor, Rural Sociology published by American Rural Sociological Association

Jianghong Li, Fiona Stanley, Eugen Mattes, Anne McMurray, Clyde Hertzman. Guest Editors of Health Sociology Review Special Issue: Social Determinants of Child Health.

Helen Leonard. Executive Committee Australian Association of Developmental Disability Medicine 2002-

Daniel McAullay. Member NHMRC Aboriginal and Torres Strait Islander Health Research Advisory Committee 2006 –

Daniel McAullay. Chair NHMRC Indigenous Health Research Panel 2006 – 2007 (member in 2008)

Daniel McAullay. Member Hearing Services Consultative Committee – Office of Hearing Services 2006 – 2008

Jonathan Foster – Postgraduate Thesis Examination Committee, School of Psychology and Behavioural Science, University of Melbourne (2008)

Anne McKenzie, Member, Consumer Health Forum of Australia (CHF), Canberra.

Anne McKenzie, Chair. Consumers Health Forum Community Quality Use of Medicines Steering Committee.

Anne McKenzie, Consumer Representative CHF, National Prescribing Service New Drugs Working Group Chair Editorial Group for Medicines Update

Anne McKenzie, Consumer Representative CHF, National Prescribing Service Pharmaceutical Decision Support Working Group.

Anne McKenzie, Consumer Representative CHF, Medicines Australia – Code of Conduct Appeals Committee.

Elizabeth Milne, NHMRC Grant Review Panel Member (2005-)

Shawn Phillips, State Delegate, Suicide Prevention Australia

Sven Silburn, Member, Australian Research Alliance for Children & Youth

Sven Silburn, Member, National Longitudinal Study of Australian Children Consortium Advisory Group 2002 – current

Steve Zubrick, National Children and Youth Statistics Advisory Committee, Australian Bureau of Statistics, Member (2003 - present)

Steve Zubrick, Member, Longitudinal Surveys Advisory Group (LSAG) (2007 – present)

Steve Zubrick, Member, Australian Families and Children Council (AFCC) (1/7/2007-30/6/2009)

Steve Zubrick, Member, VicHealth Indigenous Advisory Committee (2008 – present)

External Committees – International

Eve Blair, Editorial Board of the Cochrane Review Group for Movement Disorders.

Eve Blair, 2006- Scientific advisory committee for 3rd International CP Meeting. Sydney, Feb 2009

Carol Bower, International Clearinghouse for Birth Defects Surveillance and Research, Chair 2007-2009.

Nick de Klerk, Member of Health Canada's Expert Panel on the Exposure-Response Characterization of Chrysotile Asbestos. 2007-8.

Ngiare Brown. Foundation member and International Steering Committee member Pacific Region Indigenous Doctors' Congress United Nations Permanent Forum on Indigenous Issues (UNPFII) Pacific Caucus 2001-

Glenys Dixon, Member of Autism Speaks International Autism Epidemiology Network Workgroup 2007-

Deborah Lehmann. Scientific Committee for 6th International Symposium on

Pneumococci & Pneumococcal Diseases

Helen Leonard. Program Committee, World Rett Syndrome Congress (2008), Chair

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 (2006-8)

Elizabeth Milne, Member, Management Committee and Coordinating Committee, Childhood Leukaemia International Consortium (2006-8)

Wendy Oddy, Treasurer, Local Organising Committee, International Society for Research into Human Milk and Lactation. International conference held in Perth, Western Australia 2004-2008.

Wendy Oddy, Executive Committee Member, International Society for Research into Human Milk and Lactation, 2008-2010.

Wendy Oddy, Member, International Society for Research into Human Milk and Lactation, since 2001.

Taylor, C. L. Member of the Child Language International Cohorts Collaboration.

Taylor, C. L. Member of the Executive Board of the International Journal of Speech-Language Pathology

Invited Presentations

Anderson, A. InterRett 6th World Rett Syndrome Congress, Paris, October 2008.

Allen, K. L., Byrne, S. M., McLean, N. J., & Davis, E. A. (2008). The cognitive-behavioural model of binge eating: Validation using prospective data from 8- to 13-year-old boys and girls. Paper delivered at the 2008 International Conference on Eating Disorders, Seattle, Washington.

Allen, K. L., Byrne, S. M., McLean, N. J., & Davis, E. A. (2008). The development of binge eating in pre-adolescent children: Results from the Childhood Growth and Development Study. Paper delivered at the 6th Annual Conference of the Australian and New Zealand Academy of Eating Disorders, Perth, Australia.

Andrews R, Leach AJ, Joseph T, Richmond P, Menzies R, Brown N, Lehmann D, McIntyre P, Carapetis J. Indigenous immunisation research in Australia: the way forward. Public Health Association of Australia 11th National Immunisation Conference 16-18 Sep 2008, Surfers Paradise Qld.

Barrow,G. Barrow J, Ormond College Cultural Competencies Meeting, Melbourne August 2008

Blair, E. Prediction or Causation: The nature of the association between maternal pre-eclampsia and cerebral palsy. AusACPDM annual meeting, Brisbane, April 12th 2008.

Blair, E. Pre-eclampisa as a risk factor for cerebral palsy. 7th international congress on early brain damage. April 26th. Bled, Slovenia. 2008.

Blair, E. Australian Cerebral Palsy Register(s): origins, problems and (some) solutions. 7th international congress on early brain damage.. April 27th. Bled, Slovenia. 2008.

Blair, E. Cerebral palsy research in Western Australia. April 28th Toulouse. France. 2008.

Bower, C. Slone Memorial Lecture, Slone Epidemiology Center, Boston University, USA, May 2008. A sorry state of affairs: Aboriginal child health in Australia. Invited institutional lecture.

Bower, C. National Fetal Alcohol Spectrum Disorder Workshop, Glenelg, SA. Strategies for preventing FASD. Invited plenary presentation and Discussion Group Facilitator.

Curran, J., Suriano, K., Phillipe, D., Byrne, S.M., Bulsara, M., & Davis, E.A. (2008). The association of family history and BMI z-score with obesity related complications in primary school aged children. Australasian Pediatric Endocrine Group, Canberra.

Curran, J., Suriano, K., Phillipe, D., Byrne, S.M., Bulsara, M., & Davis, E.A. (2008). The association of family history and BMI z-score with obesity related complications in primary school aged children. Princess Margaret Hospital Research and Advances, Perth.

de Klerk, N. Childhood leukaemia, intrauterine growth and diet. ICNIRP/WHO/BfS International Nick de Klerk,Workshop on Risk Factors for Childhood Leukemia, Berlin, 2008.

de Klerk, N. Case-control study of mesothelioma in subjects with no known exposure to asbestos. Nick de Klerk,International Mesothelioma Interest Group Conference, Amsterdam, 2008

de Klerk, N. Western Australian Twins: Birth weight, Zygosity and Gestation. Australian Twin Research Day, Perth, 2008.

de Klerk, N. Western Australian Twin Register: what it does, how it works, and how you can help. Australian Multiple Birth Association Annual Convention, Perth, 2008.

D'Antoine H, Payne J, Peadon E, Henley N, O'Leary C, Bartu A, Bower C, Elliott E on behalf of the Alcohol and Pregnancy Steering Committee. Alcohol use in pregnancy: Patterns, Effects and Research. March 2008. Aboriginal Health Council WA Health Forum.

D'Antoine H. Aboriginal women's knowledge, attitudes and practice. National Fetal Alcohol Spectrum Disorder

Workshop, Adelaide, August 2008.

D'Antoine H. Alcohol and Pregnancy: Implications for Education. Challis Early Childhood Education Centre and Primary School, Perth. July 2008

D'Antoine H. Alcohol and Pregnancy: It affects all of us. We grow them up: Learning Festival (for East Arnhem Land), Darwin, Northern Territory, 28-29th April 2008.

D'Antoine H. Aboriginal women's knowledge, attitudes and practice. National Fetal Alcohol Spectrum Disorder Workshop, Adelaide, August 2008.

D'Antoine H. Aboriginal women's knowledge, attitudes and practice. National Fetal Alcohol Spectrum Disorder Workshop, Adelaide, August 2008.

D'Antoine H. Alcohol and Pregnancy: Implications for Education. Challis Early Childhood Education Centre and Primary School, Perth. July 2008.

D'Antoine H. Alcohol and Pregnancy: It affects all of us. We grow them up: Learning Festival (for East Arnhem Land), Darwin, Northern Territory, 28-29th April 2008.

D'Antoine H. Alcohol and Pregnancy: WA Aboriginal women's knowledge, attitudes and practice. Kimberly Aboriginal Health Research Forum, Broome, 31st October 2008.

D'Antoine H. Alcohol and Pregnancy: WA Aboriginal women's knowledge, attitudes and practice. Goldfields Health Service (Ware Street), Kalgoorlie, 5th November 2008.

D'Antoine H. Alcohol and Pregnancy: WA Aboriginal women's knowledge, attitudes and practice. Goldfields Health Service (The Palms), Kalgoorlie, 7th November 2008.

D'Antoine H. Alcohol and Pregnancy: We can all do something. Disability Services Commission: Country Services Annual Forum. May 2008.

D'Antoine H. Alcohol use in Pregnancy: We all have a role to play. Aboriginal Health Promotion Video Conferencing Series, Perth. May 2008.

D'Antoine H. Child Development Services: Some relevant information. Child Development Services, Department of Health WA. (invited speaker). April 2008.

D'Antoine H. Effects alcohol use in pregnancy and current directions. Videoconference link up from Kalgoorlie, Menzies, Leonora, Laverton, Esperance. February 2008.

D'Antoine H. Fetal Alcohol Spectrum Disorder and relevance for Educators, West Kimberley Remote Teachers Workshop, Broome, 1st November 2008.

D'Antoine H. Fetal Alcohol Spectrum Disorder Program of Research. Kalgoorlie Regional Hospital (allied health professionals). February 2008.

D'Antoine H. Fetal Alcohol Spectrum Disorder, Department of Child Protection, Derby, 3rd November 2008.

D'Antoine H. Fetal Alcohol Spectrum Disorder. Kalgoorlie Regional Department of Education Regional Office, Broome. March 2008.

D'Antoine H. Fetal Alcohol Spectrum Disorder: Primary and Secondary Prevention – The Aboriginal Story. Aboriginal Health Conference, Rural Health West, Perth. June 2008

D'Antoine H. Health Economics and Aboriginal Health. University of Postgraduate students: Health Systems and Economics Unit. September 2008. (guest lecturer).

D'Antoine H. Indigenous child health issues: A thumbnail sketch. Princess Margaret Hospital Multicultural Study Day, Perth, 21st November 2008.

D'Antoine H. Indigenous Mobile Playgroup mini conference (Mobile Muster) for the Indigenous Professional Support Unit Yorganop Child Care Aboriginal Corporation. 27th November 2008. Invited presentation.

Foster, J. Glucose and Memory. International Congress of Psychology, Berlin, July 2008.

Foster, J. The e2 and e4 alleles in the AIBL study. CSIRO-AIBL flagship meeting, Melbourne, October 2008.

Hansen, J. WA Twin Register: what we have and how you can get it! Twin Research Symposium, Perth, November 2008.

Hayward,C. Keynote, Unions WA International Women's Day Celebration, Perth, March 2008

Hayward, C, Keynote, Aboriginal Women's Network International Women's Day Celebration, Perth, March 2008

Hayward, C, Keynote, World Congress of Health Professionals Conference, Perth, March 2008

Hayward, C. Panel Presentation, Australasian Lymphology Association Conference, Fremantle, March 2008

Hayward, C. Keynote, Australasian Lymphology Association Conference, Fremantle, March 2008

Hayward, C. Keynote, Healthy for Life Conference, Adelaide, April 2008

Hayward, C. Keynote, WA Council of Social Services Conference, Perth, May 2008

Hayward, C. Acknowledgement of Country, WA Citizen of the Year Awards Presentation Ceremony, Burswood, June 2008

Hayward, C. Concurrent Session Presentation, National Native Title

Conference, Perth, June 2008

Hayward, C. Keynote, National Native Title Conference, Perth, June 2008

Hayward, C. Keynote, City of Joondalup NAIDOC Celebration, Joondalup, July 2008

Hayward, C. Keynote, FaHCSIA NAIDOC Celebration, Perth, July 2008

Hayward, C. Panel Presentation. Lotterywest Board Strategic Planning Process, Victoria Park, July 2008

Hayward, C. Keynote, WA Department of Education and Training Aboriginal Teachers and Administrators Conference, The Vines, September 2008

Hayward, C. Keynote, Pilbara Women's Conference, Port Hedland, September 2008

Hayward, C. Acknowledgement of Country, WA Awards for Excellence in Mental Health Presentation, Perth, October 2008

Hayward, C. Keynote, National Breast Cancer Week Celebrations, Burswood, October, 2008

Hayward, C. Acknowledgement of Country, Spirit of Our Streets Celebration, Perth, October 2008

Hayward, C. Acknowledgement of Country, Reunion of WA Citizen of the Year Award Winners, Perth, October 2008

Hayward, C. Mercy Care Annual Catherine McAuley Oration, Mount Lawley, October 2008

Hayward, C. Keynote, World Indigenous Peoples Conference on Education, Melbourne, December 2008

Hayward, C, Barrow, H , Ferguson-Hill, S. I-AEDI, World Indigenous Peoples Conference on Education, Melbourne, December 2008

Li, J; Stanley, F. Modernity's Paradox: Structural determinants of child health and wellbeing, Bielefeld University, Germany April 25 2008.

Li, J. Reasons for drug initiation in adolescents in Yunnan, China, University of Zurich, Switzerland April 22 2008.

Laing, I. The contribution of immune gene variations to the age of first pneumonia in children from the highlands of Papua New Guinea. Australian Respiratory Council, Sydney NSW Dec 10 2008.

Leonard, H. The International Autism Epidemiology Network Registry Workgroup meeting. Autism Speaks, London, May 2008.Invited discussant-accommodation and travel costs paid.

Leonard, H. Clinical variability and relationship with genotype in Rett syndrome:insights from AussieRett and InterRett. Monitoring function in Rett syndrome for Clinical Trials RettSearch Symposium- Clinical Trials in Rett syndrome, Chicago, June 2008.

Leonard, H. Relationship between Genotype and Phenotype in Rett syndrome 6th World Rett Syndrome Congress, Paris, October 2008.

Mattes E, Hickey M. Androgens and mental health. Australian Rotary Health, Business Leaders Luncheon, Perth Western Australia, 12 February 2009.

McKenzie, A. Good Practice Showcase - developing an organisational strategy for involvement, Involving People in Research Symposium. Perth. March 2008

McKenzie, A. Consumer and Community Participation in Research – an organisational strategy for engagement. WA DoH Clinical Immunology Network Research Forum. Perth. April 2008

McKenzie, A. Consumer and community participation in health and medical research. Health Consumers' Council WA Health Issues Group. Perth. June 2008

McKenzie, A. An organisational strategy for involvement. INVOLVE Conference Nottingham, UK. Nov 2008

McKenzie, A. Panel Member, DoHA National Medicines Policy Conference. Canberra. Dec 2008

Milne, E. Diet, intra-uterine growth and childhood leukaemia. 2nd Causes and Prevention of Childhood Leukaemia Conference, Institute of Child Health, London, UK, April 2008.

Milne, E. AUS-ALL: Foetal growth and risk of childhood ALL. Australian and New Zealand Children's Haematology/ Oncology Group Annual Scientific Meeting, Perth, May 2008

Milne, E. Childhood Cancer Epidemiology. The Cancer Council WA 50th Anniversary Research Dinner, Parmelia Hilton Hotel, Perth March 2008.

Moore, H. Epidemiological perspectives of lower respiratory tract infections in Western Australian children. National Public Health Institute, Helsinki, Finland, June 2008.

Oddy, W. Emerging Role of Functional Proteins in Milk symposium, San Francisco, USA, October 2008.

Oddy, W. 3rd International Brain Phospholipids conference September 2008, "Fatty acids and depression project", Oslo, Norway.

O'Donnell, M., Nassar, N., Leonard, H., Hagan, R., Mathews, R., Patterson, Y., Stanley, F. "Increasing Prevalence of Neonatal Withdrawal Syndrome: Population Study of Maternal Factors and Child Protection Involvement." 20 min oral presentation at the Impact of Parental Drug and Alcohol Use on Pregnancy, Newborns and Infants Working Party meeting November 2008.

O'Leary, C. National Fetal Alcohol Spectrum Disorder Workshop, Glenelg, SA. Alcohol and Pregnancy Policy and

Guidelines: The need for consistency, dissemination, and comprehensiveness

O'Leary, C. Curtin University – February and July 2008. Postgraduate Child and School Health Nursing Students; Alcohol in Australia : The impact on children

O'Leary, C. Alcohol in Australia: The impact on children. Invited speaker, Staff development workshop, Princess Margaret Hospital for Children, Perth. March 4, 2008.

O'Sullivan, T. Dietitians Association of Australia 26th National Conference, Gold Coast, May 2008 'A Good Quality Breakfast is Associated with Better Mental Health in Adolescence' (oral presentation).

O'Sullivan, T. Dietitians Association of Australia 26th National Conference, Gold Coast, May 2008 'Glycemic Intake and Association with Obesity in a Population Based Early Adolescent Cohort' (oral presentation).

Robinson, M. Asia-Pacific Academic Consortium for Public Health (APACPH) Conference (Kuala Lumpur, Malaysia): 7th-9th November 2008 "Hypertensive diseases of pregnancy and the development of behavioural problems in childhood and adolescence: The Western Australian Pregnancy Cohort Study"

Robinson, M. International Society for the Study of Behavioural Development 20th Biennial Meeting (Wurzburg, Germany): 13th-17th July 2008 "Hypertensive diseases of pregnancy and the development of behavioural problems in childhood and adolescence: The Western Australian Pregnancy Cohort Study"

Robinson, M. School of Psychology, The University of Western Australia (Perth, WA): 17th October 2008 "Hypertensive diseases of pregnancy and the development of behavioural problems in childhood and adolescence: The Western Australian Pregnancy Cohort Study"

Robinson, M. Telethon Institute for Child Health Research Annual Research Conference (Perth, WA): 12th March 2008 "The association between diet and lifestyle factors and mental health in early adolescence"

Shepherd, C, Walker, R Communities for Children (CfC) Facilitating Partners Webinar, ARACY, June 2008.

Shepherd, C. Challis Primary School Staff Professional Development Day, TICHR, July 2008.

Silburn, S. and Walker, R. Community Learning for Parenthood- Issues and implications for policy Presentation at the Australian Research Alliance for Children and Youth (ARACY) National Access Grid Seminar, Perth March 2008.

Silburn, S. Keynote address. National Public Health Reform Summit, 'Engaging, enabling and supporting communities for health and well being'. Securing a more sustainable future for Australian children. Sydney Harbour Marriott. 7-8 August 2008.

Silburn, S., Brinkman, S., Hayward, C., Ferguson-Hil, S., Cromb, E. The I-AEDI Project: Validation of the Cultural Adaptation of the Australian Early Development Index (AEDI) for Use With Indigenous Children. 10th Australian Institute of Family Studies Conference. 'Families through life'. 9-11 July 2008. Melbourne Exhibition Centre.

Silburn, S. Key note Address on the I-AEDI project at the launch of the Pilbara, Communities for Children Television Launch, Karratha, November 2008

Stanley, F. Key Note Address Our Community, Our Youth Our Future, Hedland Youth Forum, March 2008

Stanley, F. "How can we harmonise privacy and use population data for public good? New Zealand International Science Festival, Dunedin, New Zealand, July, 2008.

Stanley, F. "Novel record linkages to improve child health and wellbeing" Florey lecture, Adelaide, 2008.

Stanley, F. How to foster and measure social inclusion. Natstats Conference, Melbourne, November, 2008.

Taylor, C. L. (November 2008). Predictors and outcomes of early language delay. Australian Multiple Birth Association National Convention, Perth, Western Australia.

Suriano, K., Curran, J., Byrne, S.M., & Davis, E.A. (2008). Sedentary behaviour is associated with increased metabolic risk in young children. Australasian Pediatric Endocrine Group, Canberra.

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Suriano K, Frazer F. Managing overweight and obesity in young people. Australian Medical Association (WA), Perth WA,

September 2008.

Taylor, C. L. (May 2008). Children with early language delay: Who are they and how can we help? Australian Multiple Birth Association (Western Australia) State Conference, Bunbury, Western Australia.

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van den Biggelaar, A. Host factors that influence vaccine responses. Tenth International Symposium on Respiratory Viral Infections. Singapore Feb 28-Mar 2 2008.

van Eekelen, A. Stress & Teenage Brain Maturation. The School of Anatomy and Human Biology, University of Western Australia, 3 June 2008.

van Eekelen, A. Adolescent brain maturation: for the better or worse? Association of Neurophysiology Technologists of Australia (ANTA) annual conference, Perth 21 November 2008.

Watt F., Byrne S.M., Gibson L.Y., Blair E., Davis E.A. (2008). Measures of adiposity for predicting mental health outcomes in children and adolescents. Poster presented at the North American Association for the Study of Obesity, Pheonix, USA.

Walker, R. The Importance of Indigenous Early Learning and Play, Wollaston Convention Centre, Mt Claremont, Western Australia. February 2008.

Walker, R, Silburn, S. Community Learning for Parenthood- Issues and implications for policy Presentation at the Australian Research Alliance for Children and Youth (ARACY) National Access Grid Seminar, Perth March 2008.

Walker, R. 'Shout Out' Forum, Presentation and co-facilitation of the Hedland Youth Leadership Council, South Hedland, WA, March. 2008.

Walker R. Doing Research in Aboriginal Contexts. Seminar for the Indigenous community Management and Development Program 3rd Year Students Centre for Aboriginal Studies, Seminar Room, Telethon Institute for Child Health Research, April 2008.

Walker, R., Shepherd, C. Engaging Indigenous Parents in Preparing their Children for School, Presentation at the Australian Research Alliance for Children and Youth (ARACY) National Access Grid Seminar, Perth, June 2008.

Walker, R. Engaging Young People in Hedland in the Research Australian Research Alliance for Childern and NSW Commissioner for Children and Young People Youth Think Tank 'Engaging Young People in Research', Sydney, November 2008.

Walker, R. Implementing the Pilbara Community AEDI results in the Pilbara, Communities for Children Television Launch, Karratha, November 2008.

Walker, R. Social Research Methods 2 day Workshop for the Pilbara Youth Leadership Council, Creating Communities and Hedland Youth Stakeholder Action Group. South Hedland, November 2008.

Zubrick, SR. Social Sciences. Australian Statistical Conference 2008. 'Celebrating Diversity'. Sofitel, Melbourne, 30 June – 3 July 2008.

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