

ANNUAL REPORT 2009

SCIENTIFIC SUPPLEMENT



PREVENTION
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1990 - 2010



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Telethon Institute for Child Health Research

What do you do when a child falls seriously ill, or suffers from a chronic disease or disability?

What do you do when you discover that a child is affected by a disorder like autism, or that they battle with anxiety or depression?

Many of us start asking questions.

What's the best treatment? Is there a cure?

Could it have been prevented? Why did this happen to my child?

For the past 20 years, scientists at the Telethon Institute for Child Health Research have been working to answer those questions that matter most to families.

Under the leadership of Professor Fiona Stanley, we pioneered an innovative approach that has brought together the best scientists from a wide range of scientific expertise to tackle these big issues from multiple angles.

It's an approach that has brought significant success in areas such as preventing birth defects, infectious diseases, childhood cancer and leukaemia, child development, disability, mental health and the issues facing Aboriginal children and their families.

Based in a purpose-built facility on the edge of the Perth CBD, the Institute has nearly 500 staff and post-graduate students focussed on improving the health and wellbeing of children. We also host around 80 honorary and visiting researchers throughout the year.

The Institute is an independent, not-for-profit organisation with strong affiliations with Western Australia's children's hospital and all the major universities.

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.



Cell Biology

Overview

Our research continues to focus upon the mechanisms that determine susceptibility and resistance to infections and allergic diseases in the respiratory tract during childhood, and in particular how these mechanisms interact to drive the development of asthma. A unifying theme in this research stems from our earlier findings that risk for development of allergy and asthma is determined primarily by factors which control the functional maturation of the immune system during early childhood. In particular we have shown that a variety of the cellular immune effector mechanisms which are suppressed in utero in order to protect the placenta from inflammatory damage are vital for protection against both infections and allergy during infancy, and the speed of their functional maturation during the preschool years is retarded in children from families with a history of allergic diseases. Much of the work of the Division is aimed at more detailed definition of these genetically determined mechanisms, with the ultimate goal of developing new early intervention strategies to reduce asthma susceptibility, ideally to permanently prevent its onset. This work includes studies on the safety and efficacy of pediatric vaccines, as many of the underlying immunological mechanisms involved relate also to asthma/allergy susceptibility. An important complementary stream of research in our Division involves animal model studies on immunoregulation of the cell populations responsible for triggering T-lymphocyte

activation in the airway mucosa during the "late phase response" in asthma. The main focus of this aspect of our research is on interactions between T-regulatory cells and the network of airway mucosal Dendritic Cells which are responsible for immune surveillance in the respiratory tract.

Aetiology and pathogenesis of atopy and asthma

Interactions between antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children

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Asthma exacerbations in children requiring hospitalisation are typically associated with viral infection, and occur predominantly amongst atopics, but the significance of these comorbidities is unknown. On the basis of earlier findings in our cohort studies we hypothesised that underlying interactions between immunoinflammatory pathways related to responses to aeroallergen and virus are involved, and that evidence of these interactions is detectable in PBMC during exacerbations. To test this hypothesis we profiled gene expression in paired PBMC samples from atopic asthmatic children collected at admission to hospital emergency with

acute severe asthma versus at subsequent convalescence, by microarray and flow cytometry. We identified exacerbation-associated activation signatures within monocyte/DC populations characteristic of the IL-4/IL-13-induced "alternatively activated (AA)" phenotype, including hyperexpression of mannoseR and IL-13R, accompanied by activation of Type-I interferon-sensitive genes and markedly increased FcERI expression. Recent findings in mice indicate that viral-induced Type-I interferon(s) mediate comparable FcERI upregulation in airway DC, markedly enhancing local Th2 cytokine responses. We therefore suggest that via a similar process, respiratory viral infection in atopic children triggers a multi-step atopy-dependent cascade which amplifies and sustains airway inflammation initiated by anti-viral immunity. This cascade comprises initial interferon-induced FcERI-mediated upregulation of airway mucosal Th2 cytokine/chemokine production utilising pre-existing IgE, resulting in programming, recruitment and subsequent local triggering of IL-4/IL-13-dependent AA monocytes. These interactions may account for the enhanced susceptibility of atopics to severe viral-induced asthma exacerbations.

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

Employing network analysis strategies to understand the allergen-driven Th2 memory response

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

This ongoing study aims at investigating the in vitro allergen-specific T cell memory response in humans utilizing microarray technology. Recent developments in network theory and statistical tools have enabled us to employ network analysis to the microarray data sets we have developed for the study of Th2-memory responses to house dust mite allergen, and this approach provides information far richer than a list of differentially expressed genes. The underlying principal of network analysis is that genes do not act in isolation, but are networked with other genes in a highly modular fashion to perform biological functions. Gene networks are organized into sets of coordinately regulated genes, known as modules, which may correspond to biological pathways. Within a module we have been able to identify a small number of "hub" genes which are highly correlated to many other genes and are thus likely to be essential for the function of the module. We applied network analysis to characterize the molecular mechanisms that underpin allergen-driven CD4+ T cell responses in human atopics, and identified a module of 71 genes comprising Th2 signature genes plus many novel genes which is upregulated in sensitized atopics compared to nonatopic control subjects. The main function of genes within the Th2-associated module included transcriptional regulation, signal transduction and proliferation. We also identified the receptors for IL2 and IL4 as hyperconnected hub genes within the

module, and demonstrated their role as key drivers in regulating the module, since targeted disruption of the IL2 and IL4 signaling pathways perturbed expression of the module genes as a whole. Finally, network analysis can identify negatively correlating genes, which may potentially act as negative regulators. We have identified several negatively correlating genes within the Th2-associated module, and we are investigating the role of IL-4 in regulating the expression of these genes. We are additionally using network analysis approaches to define potential differences between Th2 memory responses in HDM-sensitized atopics who are asymptomatic versus those with severe asthma.

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

Th2-associated immunity to bacteria in asthma in teenagers and susceptibility to asthma: findings from the W.A. Pregnancy Cohort Asthma and Allergy study.

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Recent indirect evidence has linked bacterial colonisation of the airways with increased risk for childhood asthma. Possibly related to this, IgE against

bacterial antigens has been reported in some asthmatics, suggesting a role for bacterial-specific Th2 immunity in disease pathogenesis. We have recently investigated the relationship between *S. aureus*-specific IgE and asthma susceptibility amongst 14-year-olds from the W.A. Pregnancy Cohort. Our preliminary findings suggest that IgE titres against *S. aureus*-derived superantigens are highest amongst atopics and are associated with risk for asthma, rhinoconjunctivitis and eczema. We are expanding these studies to include assessment of IgE titres against cell-surface antigens from *H. influenzae* and *S. pneumoniae*, based on recent findings from the TICHOR Division of Molecular Biotechnology which suggest that these organisms may also be implicated in the pathogenesis of chronic airways inflammation in children.

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

Association of single-nucleotide polymorphisms in the β_2 -adrenoreceptor with asthma in 14-year-olds.

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β_2 -adrenergic receptors are involved in physiologic responses in the lung including bronchodilation and bronchoprotection, and may play an important role in the

pathophysiology of asthma. Medications targeting β_2 -adrenergic receptors, known as β -agonists, cause immediate reversal of airway narrowing, and are among the most commonly used asthma medications. The gene encoding the β_2 -adrenergic receptor, called ADRB2, is extremely polymorphic; previous studies examining whether single nucleotide polymorphisms (SNPs) in this gene are associated with asthma have given conflicting results. We have undertaken preliminary analyses to determine whether SNPs in the ADRB2 gene are associated with asthma or bronchial hyperresponsiveness (BHR) in subjects from the W.A. Pregnancy Cohort at ages 6 and 14. We have genotype information for 3 ADRB2 SNPs within the cohort: ADRB2-565, located 5' of transcription; ADRB2-1633, a coding region mutation causing a change from Arginine to Glycine at codon 16 (Arg16Gly); ADRB2-1839, a coding mutation which does not result in a change in amino acid from Leucine at codon 84. Our initial findings suggest that at age 14 mutated ADRB2-565 was significantly protective against asthma in atopics, as was mutated ADRB2-1633. In contrast, mutated ADRB2-1839 appeared to be a significant risk factor for current asthma at age 14 in the whole population. Multivariate regression analyses are in progress to integrate these data with immunophenotypes in our study population, and followup studies have been initiated with collaborators in the US to ascertain whether similar relationships can be found between asthma risk and ADRB2 gene polymorphisms in the Tucson

children's asthma cohort.

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

Association of maternal smoking in pregnancy with respiratory outcomes at age 14 years.

E.M. Hollams, P.G. Holt and P.D. Sly.

Numerous studies have suggested that maternal smoking during pregnancy may have adverse effects on children that persist into later life. Information on maternal smoking in pregnancy (MSP) is available for 1099 of the 1380 14-year-olds that we have studied in the W.A. Pregnancy Cohort Asthma and Allergy Study. We have therefore examined whether MSP is associated with changes in respiratory function, in vitro immune function, or with development of allergy. We found that asthma was significantly more frequent amongst MSP+ teenagers; there was likewise a markedly increased prevalence of wheeze, exercise-induced wheeze and poor lung function (defined as FEV1/FVC<80) in this group. Body mass index was increased in the MSP+ group, in agreement with previous studies, and levels of circulating neutrophils were also increased; we did not see a difference in in-vitro immune response capacity associated with MSP status. Univariate logistic regression analyses identified MSP as a risk factor for asthma, wheeze, exercise-induced wheeze and poor lung function within the 14-year-olds. We examined whether MSP is a major risk

factor for these conditions when added to other biological markers in multivariate regressions. MSP significantly increased the risk for current asthma amongst the whole population, along with markers of inflammation and allergy, reduced IL-12 production, enhanced immune responses to allergen and mitogen, and increased BHR. Similar risk factors were observed for current wheeze and exercise-induced wheeze. Analyses are ongoing.

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

Toll-like receptor 7 function is reduced in adolescents with asthma

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Anti-viral innate immune responses may be impaired in asthma, though the mechanisms are not well understood. Toll-like receptors (TLRs) 7 and 3 are particularly relevant for initiating responses to common respiratory viruses, as they recognise single-stranded viral RNA and double-stranded viral RNA respectively. We investigated TLR7 and TLR3 function in adolescent asthma by studying a subset of 14-year-old subjects from the W.A. Pregnancy Cohort Asthma and Allergy Study. We tested blood mononuclear cells

obtained from atopic asthmatic, atopic non-asthmatic and healthy non-atopic individuals, by stimulation with the TLR7 agonist imiquimod and the TLR3 agonist poly I:C, and resultant gene expression of relevant targets was measured at the mRNA or protein level. We measured mRNA levels of the immune-regulatory cytokine IL-10, IRF7 (identified as a "master regulator" of antiviral immunity) and two interferon-sensitive genes encoding anti-viral proteins: myxovirus resistance protein A (MxA) and 2'5' oligoadenylate synthetase (OAS). We measured IFN- γ inducible cytokine protein 10 (IP-10) secreted by cultured PBMC (IP-10 acts as a chemoattractant for activated Th1 cells and natural killer cells and has been closely linked to viral exacerbations of asthma), in addition to the cytokines IL-6 and IL-10. TLR7-induced MXA and OAS mRNA levels were significantly lower in subjects with asthma compared to healthy subjects ($p=0.041$ and $p=0.003$ respectively), as were protein levels of IP-10 ($p=0.001$). There was a significant negative correlation between total serum IgE and IP-10 following TLR7 stimulation. In contrast, TLR3-induced responses did not vary with asthma or atopy, and IL-10 mRNA and IL-6 protein levels were similar in asthmatic and control subjects. These findings suggest that TLR7 function is reduced in adolescents with asthma, which may contribute to susceptibility to respiratory viral infections.

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

Prediction of risk for respiratory infections in atopic family history positive children by analysis of cytokine production profiles in cord blood

G. Zhang, J. Rowe, M. Kusel, A. Bosco, K.L. McKenna, N. de Klerk, P.D. Sly and P.G. Holt

Respiratory infections in early life are associated with risk for wheezing bronchiolitis, and for subsequent development of persistent asthma, especially in children at high risk of atopy by virtue of positive family history. The underlying mechanisms are unknown, but are suspected to involve imbalance(s) in host defense responses against pathogens stemming from functional immaturity of the immune system in this age group, particularly during infancy. To test this hypothesis we have recently assessed the capacity of cord blood mononuclear cells to produce eosinophil-trophic IL-5, and the potent anti-inflammatory cytokine IL-10, as potential predictors of risk for infection in early life. We prospectively followed a cohort of 198 HR children to age 5 years, recording every acute respiratory infection (ARI) episode and classifying them by severity. We measured cord blood T-cell capacity to produce IL-10 and IL-5, and related these functions to subsequent infection history. IL-10 and IL-5 were associated respectively with resistance versus susceptibility to infections. The greatest contrasting effects of these two cytokines were seen when they were considered in combination by generating IL-10:IL-5 response ratios for each subject.

The low IL-10/high IL-5 T-cell response phenotype was strongly associated with susceptibility to all grades of acute respiratory infection, relative to the more resistant high IL-10/low IL-5 phenotype. This suggests that excessive production of IL-5 by T-cells at birth is associated with heightened risk for subsequent severe respiratory infections, and this risk is attenuated by concomitant IL-10 production. The underlying mechanisms may involve IL-10-mediated feedback inhibition of IL-5-dependent eosinophil-induced inflammation, which is a common feature of host-anti-viral responses in early life. However the low IL-10/high IL-5 high risk phenotype may be part of a more complex underlying immunophenotype, and we have additionally investigated this possibility by re-profiling cytokine responses in neonatal cells from children at the two extremities of the IL-10/IL-5 response range by microarray. Our findings suggest that an additional potentially important element in the high-infection-susceptibility phenotype is decreased capacity to produce IL-21.

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

Pediatric Vaccine Studies

Neonatal immunization with pneumococcal conjugate vaccine in Papua New Guinea

A.H.J. van den Biggelaar, M. Nadal-Sims, C. Devitt and Patrick G. Holt in collaboration

with D. Lehmann (Population Sciences, TICHR), P. Richmond (UWA School of Paediatrics and Child Health), and S. Phuanokoonnon, 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 were 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. Comprehensive immune phenotyping by protein cytokine analysis, microarray and qRT-PCR demonstrated that cellular memory immune responses to the vaccine protein carrier CRM197 were similar at 9 months of age in children that had been vaccinated either according to the neonatal or infant immunization schedule. In accordance, analysis of circulating vaccine serotype-specific IgG antibodies performed by W. Pomat at the PNG Institute of Medical Research demonstrated high and similar responses in children vaccinated according to either schedule. These findings indicate that neonatal 7vPCV vaccination is immunogenic in high-risk PNG infants.

Furthermore, findings that only few local side effects to 7vPCV vaccination were observed and that there was not an increase in serious adverse events in either of the vaccination groups demonstrate the safety of neonatal and infant 7vPCV vaccination in this population. Now that we have demonstrated that neonatal 7vPCV is safe and immunogenic, large-scale clinical trials can be initiated to demonstrate the efficacy of neonatal vaccination in high-risk populations.

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

Immune ontogeny in infants in the developing and developed world

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

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. The aim of this study is to identify major differences in neonatal immune function between children born in a low (Papua

New Guinea, PNG) compared to high-income setting (Australia, AUS) as a “net outcome of multiple risk factors”, hereby acknowledging the heterogeneity of the in utero environment of unborn children in these very different settings. Our findings demonstrate that the proliferation capacity of PNG cord naïve T cells (CD4+CD25-CD127+) is significantly lower and delayed compared to AUS naïve T cells, which appears to be due to yet unidentified functional deficiencies in the T-cell but more strongly in the APC compartment. Furthermore, PNG and AUS cord regulatory T-cells have a similar capacity to suppress T-cell proliferation, however, in autologous cell cultures this suppressor function of PNG cord Tregs can not be observed, probably due to a limitation of T-cell proliferation by PNG cord APC. Further studies will be undertaken to further identify the pathways that are responsible for the difference in PNG versus AUS cord APC function.

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

Host factors influencing the ontogeny of innate immune responses in Papua New Guinean infants

A.H.J. van den Biggelaar, M. Nadal-Sims, C. Devitt and P.G. Holt in collaboration with P. Franklin, M. Tulic, S.L. Prescott (UWA School of Paediatrics and Child Health) and W. Pomat, D. Stanicic, W. Kirarock and S.

Phuanokoonnon (Papua New Guinea Institute of Medical Research)

The development of protective, balanced adaptive immune responses in later childhood are to a certain extent determined by the activity of the innate immune system at birth and early infancy. This implies that the competence of vaccines and in particular vaccine adjuvant depend on the status of the innate immune system at the time of administration. This study aims to examine the effect of three major environmental risk factors in Papua New Guinea, namely malaria infections, intestinal infections and biomass fuel exposure, on neonatal and subsequent infant innate immune function. In the highlands of Papua New Guinea, 82% of the pregnant women enrolled in this study (169/206) were found to be infected with one or multiple intestinal parasites during pregnancy, of which infections with the protozoa *Entamoeba histolytica* (43%) or *Gardia lamblia* (38%) were the most frequent. Newborns whose mothers had been infected with *E. histolytica* during pregnancy demonstrated reduced responses to ASC inflammasome signaling (PolydAdT). In contrast, infections with *G. lamblia* during pregnancy were associated with an enhanced activity of the neonatal innate immune system in response to the vaccine adjuvants Monophosphoryl Lipid A and Alum as well as to viral signals including Poly:IC (double stranded viral RNA) and RSV (respiratory syncytial virus) stimulation. These first findings indicate that the response of the neonatal innate system to vaccine adjuvants and pathogens

can be affected by maternal intestinal protozoa infections. Further studies will be performed to examine the longitudinal effect of these intestinal infections on the development of the innate immune system in the first year of life. And further analysis will be performed to study the effects of malaria infections in pregnancy and indoor air pollution.

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

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.

Pertussis, or Whooping cough, is currently epidemic in Australia, even though effective vaccines are available and recommended for infants from 2 months of age, pre-schoolers, adolescents and adults. Young infants are most at risk of contracting pertussis and experience more severe disease; there have been 3 recent deaths from pertussis in Australia, all in children under 6 months of age, too young to be fully immunised against pertussis. One strategy that we have been investigating to combat this issue is to vaccinate babies soon after they are born with pertussis vaccine to induce a protective immune response in the crucial first 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 and four years of age. Cell-mediated immunity has been measured in a subset of available subjects and the results show that Th2 cytokine production in response to pertussis vaccine antigens persists through 2 years and to 4 years of age and is boosted by the 4 year preschool booster pertussis vaccination in children immunised at birth, compared with children who received the standard schedule.

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

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 Trial has now closed, and follow-up appointments completed. We aimed to determine the effects of the removal of the 18 month booster dose of Diphtheria, Tetanus, acellular Pertussis, and inactivated poliovirus vaccine (DTaP-IPV), in particular the rates of local reactions to subsequent booster DTaP at 4 years, as well as humoral and cell-mediated immunity to the vaccine components. The rates of large local reactions to the preschool booster dose in 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. A subset of subjects were separated into groups depending on the size of the swelling and redness at the injection site of the preschool DTaP booster; a group of 22 without any reaction (non-reactors) and 16 with a reaction of 40 mm or greater (reactors).

We found that reactors and non-reactors did not differ in their cell mediated immune response, as measured by cytokine production in response to vaccine antigens. Further investigations into the injection site inflammation by microarray technology are currently being analysed. Preliminary data indicate that the response to pertussis vaccination involves both Th1 and Th2 T cell memory pathways.

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

Animal Model Studies

Rat model of allergic airways inflammation

D.H. Strickland, A. Larcombe and P.G. Holt

To elucidate the central mechanisms that underpin expression of atopic asthma at the target tissue level, and hence regulation of the maintenance of "normal" function in the airways, we have developed a unique rat model featuring two inbred rat strains which closely approximate human "high allergy risk - HR" and "low allergy risk - LR" phenotypes. We have established 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, sensitized HR animals mount exaggerated airway responses such that the outcome to repeated aerosol challenge is a more persistent and severe form of inflammatory 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 and function of cells capable of regulating the inflammatory airways response within the airway mucosa. Moreover, our experimental data also suggests a series of abnormalities in the functions of other major cellular players associated with both the development and expression of disease, namely airway mucosal dendritic cells (AMDC) and T helper cells, and further that these abnormalities are restricted to respiratory tissues. Our 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.

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

Therapeutic boosting of airway mucosal Treg networks

D.H. Strickland, A. Larcombe and P.G. Holt

The maintenance of normal respiratory function and control of asthma exacerbations is linked to a regulatory T cell (Treg) network that operates within the airway mucosal microenvironment. In the experimental probiotic literature recent studies have suggested that oral administration of microbial stimuli may in some situations result in "boosted" local gastrointestinal tract (GIT) as well as systemic levels of certain types of Treg activity. In an ongoing collaboration with OM PHARMA (Geneva) these studies are investigating the applicability of these findings to the control of allergic airways inflammation. 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. Our results indicate that repeated feeding of normal or sensitised 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. Sensitised LR animals that have undergone the treatment strategy and are subsequently exposed to aeroallergen challenge (i.e. in animals with "pre-boosted" airway regulatory cell compartment defences) display

marked attenuation of the magnitude of the resulting lung inflammatory response and the duration of ensuing airways hyperresponsiveness (AHR). 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.

This research is funded by the National Health and Medical Research Council of Australia and OM PHARMA (Geneva)

Airway mucosal dendritic cell and CD4+ T cell function in a mouse model of chronic aeroallergen exposure

V. Fear, J. Burchell, M.E. Wikstrom, S. Lai, D. Turner, P.D. Sly, P.G. Holt, D.H. Strickland and P. Stumbles

Chronic aeroallergen exposure is known to limit allergen-specific T cell responses and airways hyperresponsiveness (AHR) in mice, however the mechanism(s) remain unclear. In these studies we examined the role of airway mucosal dendritic cells (AMDC) and their subsets in this process using BALB/c mice sensitised to ovalbumin (OVA) and challenged with multi-OVA aerosol exposures using a protocol known to increase airway CD25+ FoxP3+ T regulatory (Treg) cell numbers and attenuate airways hyperresponsiveness.

Allergen capture by AMDC subsets, traffic to airway draining lymph nodes (ADLN) and antigen presentation to OVA-specific CD4+ T cells were assessed in vivo and in vitro. OVA-specific CD4+ T cell proliferation was markedly restricted in the airways and ADLN of multi-OVA aerosol mice, which could be restored by adoptive transfer of OVA-loaded and activated bone marrow DC. OVA capture by CD11b+ and CD11b- AMDC subsets was downregulated after multi-OVA aerosol and similar effects were observed using soluble dextran in place of OVA. OVA uptake by CD8a- CD11b- and CD8a+ CD11b+ ADLN DC subsets was decreased 24 hours after multi-OVA aerosol, which was increased following depletion of CD25+ T cells. Further, bone marrow DC cultured from multi-OVA exposed mice were less able to present antigen to OVA-specific CD4+ T cells in vitro. These data indicate that suppression of allergen-specific CD4+ T cell responses following chronic aeroallergen exposure is mediated through attenuation of AMDC function via a multifactorial process of non-specific down-regulation of protein capture and presentation, T regulatory cell inhibition and modulation of bone marrow DC precursor maturation.

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

Mechanisms mediating chemokine receptor expression on CD4+ T cell homing to the respiratory tract

K. Wijkvist, M.E. Wikstrom, D.H. Strickland and P.Stumbles

CD4+ T cells are crucial players in the immune response of the respiratory tract. When an allergen is inhaled, a cascade of events takes place leading to the activation of CD4+ T cells in the draining lymph nodes. A proportion of these activated cells appears to be programmed to migrate out of the lymph nodes and travel (or home) to the respiratory tract where they can direct the local immune response. We previously identified several genes for chemokine receptors were upregulated in lung homing CD4+ T cells including CCR4, CCR5, and CCR8. Work during 2009 started to identify the cell types responsible for inducing the expression of CCR4 and CCR8, particularly subsets of dendritic cells (DC) in airway draining lymph nodes. In vitro culture systems were established using flow-cytometry purified CD8a- and CD8a+ DC from lymph nodes of aeroallergen (ovalbumin) exposed mice together with purified CD4+ T cells from DO11.10 transgenic TCR mice specific for ovalbumin. Both subsets of DC were capable of stimulating CD4 T cells in vitro, although CD8a- DC were more efficient. Both CCR4 and CCR8 were induced by lymph node DC and work is now continuing to determine the effect of antigen dose and timing on this response.

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

The role of the integrin CD103 in development of airways hyperresponsiveness

V. Fear, K. Wijkvist, M.E. Wikstrom, S. Lai, G. Zosky, P.D. Sly, P.G. Holt, D.H. Strickland and P. Stumbles

CD103 is the a chain of integrin aEb7, an adhesion molecule that mediates T cell binding to epithelial cells via E-cadherin. In humans, CD103 is also preferentially expressed on CD4+ and CD8+ T cells in gut, where up to 80% of T cells can be CD103+ compared to less than 5% of T cells in peripheral blood. CD103 expression has been characterized in mice in great detail, where the majority (90%) of intraepithelial T cells in the gut and a large proportion (40-50%) of mucosal T cells are CD103+, compared to a small proportion (<15%) of splenic or blood T cells. CD103-expressing DCs have been associated with T cell immunity at other barrier sites such as the intestine and skin. However, apart from knowing that CD103 and CD11b expressing AMDC subsets exist, we have little knowledge of their role in the cycle of inhaled antigen capture, processing and delivery to airway draining lymph nodes (DLN). Our initial studies have examined the development of airways hyperresponsiveness (AHR) in CD103 knock-out mice (CD103 KO), where we have shown that these mice development significantly less AHR than wild-type control mice. Interestingly, CD103 KO mice still developed an airways inflammatory response characterised by eosinophil infiltration indicated that

the mice had been sensitised to the allergen. To our knowledge this is the first demonstration of this effect, and raises the question of how this response is being mediated. Initial studies have shown that the proportion of activated/memory T cells entering the lungs and airways is the same in CD103 KO and wild-type mice, suggesting that T cell recruitment into airways is not the governing factor in AHR development in this model. However, naive T cell numbers in draining lymph nodes were increased in CD103 KO mice suggesting that T cell retention in DLN may play a role. Work is continuing on characterising this response, with focus on further characterising the inflammatory response in CD103 KO mice in terms of cytokine production and other potential regulatory T cell or other cell-type responses.

This work was funded by the Asthma Foundation of W.A.

Staff and Students

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External Committees

International

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

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

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

National

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

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

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

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

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

Invited Presentations 2009

Patrick Holt, Plenary Speaker: Prevention and treatment of atopic asthma: new concepts and new targets – 2nd International Singapore Symposium of Immunology, Singapore.

Patrick Holt, Plenary Speaker: Early life events that influence allergic status – Keystone Symposium on Allergy and Asthma, Keystone.

Patrick Holt, Symposium Speaker: Rationale for prevention of allergy with allergens – the Mucosal Tolerance phenomenon. American Academy of Allergy, Asthma and Immunology Congress, Washington.

Patrick Holt, Workshop Participant/ Chair: Postnatal maturation of immune competence during infancy – Immunology of Malaria Workshop, NIH, Bethesda.

Patrick Holt, Workshop Presenter: Targeting RSV for primary prevention of asthma – Medimmune/AstraZeneca Workshop, Madrid.

Patrick Holt, Symposium Speaker: Interactions between innate immunity and IgE in acute and chronic asthma – European Academy of Allergy and Clinical

Immunology, Warsaw.

Patrick Holt, Workshop Participant: Interactions between the immune system and the microbial environment in asthma pathogenesis – Dahlem Workshop on Inflammation and Infection, Berlin.

Patrick Holt, Workshop Participant: Treatment targets for control of asthma initiation and progression in childhood – AstraZeneca International Workshop, Stresa.

Patrick Holt, Workshop Presenter: Interactions between anti-microbial and atopic inflammatory pathways in chronic respiratory diseases – MedImmune Workshop on COPD pathogenesis, Washington.

Patrick Holt, Workshop Participant: Asthma phenotypes and drug target development – Merck, New Jersey.

Patrick Holt, Harvard Medical School, Brigham and Women's Hospital, Boston. K. Frank Austen Lecture – Programming the persistent atopic asthma phenotype during childhood.

Patrick Holt, Children's Memorial Hospital, Chicago. The role of virus-induced innate immunity in the pathogenesis of atopic asthma in children.

Patrick Holt, Harvard School of Public Health, Boston. Distinguished Lecture Series in Public Health – Aetiology and pathogenesis of asthma.

Patrick Holt, Merck, Boston. Strategic opportunities for asthma treatment and

prevention.

Patrick Holt, Novartis, Horsham. Viruses, IgE and asthma.

Patrick Holt, GlaxoSmithKline, Stevenage. Viral induced asthma exacerbations in atopics – treatment implications.

Patrick Holt, International Vaccine Institute, Seoul. Aetiology and pathogenesis of atopic asthma.

Patrick Holt, International Vaccine Institute, Seoul. New approaches to asthma prevention derived from genomics-based studies.

Patrick Holt, International Vaccine Institute, Seoul. The role of dendritic cells in regulation of T-cell immunity in the lung – the asthma late-phase response as a paradigm.

Patrick Holt, ALK Abello, Copenhagen. Interactions between atopy and viral infection in asthma pathogenesis.

Anita van den Biggelaar, Dahlem Konferenzen on Infection, Inflammation and Chronic Inflammatory Disorders: Common and Divergent Solutions to Problems at the host-Environment Interface, Berlin.

Anita van den Biggelaar, Seminar presented at the Pasteur Institute (Dept of Infection & Epidemiology and Dept of Immunology) in Paris, France.

Anita van den Biggelaar, Seminar presented at the Institute of Immunology and Infection Research, University of Edinburgh, Edinburgh, UK.

Anita van den Biggelaar, Seminar presented at the Centre for Respiratory Infection, National Heart and Lung Institute, Imperial College, London, UK.

Deborah Strickland, Australian Society for Medical Research. Panel Member, Perth, Australia.

Phil Stumbles, European Respiratory Society Annual Congress, Vienna, Austria. Antigen Capture and Presentation by Airway Dendritic Cells is Attenuated in Mice Following Chronic Aero-allergen Exposure.

Olivia White, FIMSA Advanced Immunology Training Course, Queensland, Australia

Olivia White, Poster Presentation, Australian Society of Immunology Annual Scientific Meeting, Queensland Australia.

Clinical Sciences

Overview

The Divisional activities centred around three main themes:

1. Asthma

- Studies on the mechanisms underlying the development of asthma, both in our cohort studies and mechanistic studies in laboratory animals. These studies are largely conducted as part of the Asthma Program grant and NHMRC project grants and involve collaboration between the teams headed by the Program grant PIs: Peter Sly (Clinical Sciences), Pat Holt (Cell Biology); Wayne Thomas (Molecular Biotechnology), Peter Le Souef (UWA School of Paediatrics and Child Health), Steve Stick (Clinical Sciences and PMH Department of Respiratory Medicine), 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 2009 include:

a. Prediction of future asthma risk in infants: We have used longitudinal data from one of our prospective cohorts to detect the presence of a strong and continuing relationship between airway responsiveness measured soon after birth and childhood asthma in mid childhood.

b. Plasmacytoid dendritic cells and susceptibility to respiratory disease in early life: We have shown that a relative deficiency of plasmacytoid dendritic cells during infancy is associated with increased susceptibility to lower respiratory tract

infections and asthma

c. Defining immunophenotypes and susceptibility factors in asthma in teenagers: We have published the most comprehensive analysis to date integrating immunophenotypes and asthma associated clinical phenotypes in teenagers, and have provided strong proof for a quantitative relationship between intensity of inhalant allergy and susceptibility to current asthma. This finding has important therapeutic implications.

- The Global Prevention of Asthma in Children (GPAC) study is funded by the Immune Tolerance Network and the National Institute of Allergy and Infectious Diseases, USA and uses oral mucosal immunoprophylaxis (hence forth known as OMIP). This project represents a major collaborative venture between Peter Sly and Pat Holt (Cell Biology), 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 any treatment-related serious adverse events, demonstrating that immunoprophylaxis in high risk children is safe. This cohort has finished treatment and the first children will complete the follow-up phase in 2010.

2. Early Detection of Lung Disease in Cystic Fibrosis

The AREST CF program (www.arestcf.org) has continued to provide new data on

the early course of lung disease in infants and young children with cystic fibrosis. Data from the group were presented at major National and International meetings during 2009, including the Australian Cystic Fibrosis Biannual Conference; The Thoracic Society of Australia and New Zealand Annual Scientific Meeting, The European Cystic Fibrosis Association Annual Scientific Meeting and the North American Cystic Fibrosis Association Annual Scientific Meeting.

The data generated by the early surveillance program have been used to propose a new clinical trial designed to prevent the onset of bronchiectasis in infants with cystic fibrosis. We hope to secure funding for this trial during 2010.

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

The Division of Clinical Sciences was designated as a WHO Collaborating Centre in July 2006. The terms of reference for the Centre are:

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

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

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

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

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 Pronczuk in Public Health and Environment.

During 2009, activities included:

- The Kwinana Child Health Study
- Development of animal models to study exposure to arsenic in drinking water and to diesel exhaust particles.
- Continued advice to help establish new birth cohorts aimed at studying the environmental contribution to respiratory health in children.

- The Centre co-sponsored and hosted the 13th International Conference of the Pacific Basin Consortium for Health and the Environment.

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

Staff Movements:

During 2009 we were sad to lose Felicity Flack, who, after 12 years with Clinical Sciences, has moved on to new challenges.

Dr. Vincenzo Cannizzaro finished his training period with Clinical Sciences during 2009 and has returned to Switzerland. We wish him the best of luck in setting up his new laboratory and group in Zurich.

We were pleased to formally welcome Peter Noble to the group. Peter has a NHMRC Peter Doherty training fellowship and spent 2008 at UWA within the Department of Physiology. We were also pleased to welcome Kat Ramsay (Ph D candidate, UWA), Michael Stutz (BSc (Hons) candidate, Murdoch University), and Catherine Boylen (BSc (Hons) candidate, Murdoch University).

Animal Models of Human Lung Disease

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 to develop rodent models of VILI in mice of various ages with and without background lung injuries or complications. In the initial studies we compared VILI in healthy infant and adult mice of different strains and found that infant mice appear to be less susceptible to VILI and that strain vastly alters the outcome. These studies were followed by experiments designed to investigate the effect of oxygen supplementation (a common strategy in intensive care) on VILI

responses in infant mice and found that oxygen supplementation had little impact on lung inflammation or function.

In 2009 our primary focus was to test the so called "two-hit" whereby the impact of mechanical ventilation is altered by the type of injury that the lung has sustained resulting in the need for mechanical ventilation. In these studies we moved to the use of infant rats, which appear to tolerate prolonged mechanical ventilation, and developed models of pneumonia, sepsis and acid aspiration. We found that the nature of the initial insult alters the inflammatory and mechanical response of the lung and that the combination of the effects of the initial insult and mechanical ventilation itself result in the poorest outcome.

This study was supported by the Swiss National Science Foundation

Arsenic induced non-malignant lung disease

Kathryn Ramsey, Peter Sly, Graeme Zosky

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

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

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

in later life. In 2009 we began studies to examine the effect of combining arsenic exposure with an additional respiratory insult using a mouse model of influenza infection. Preliminary results from these studies suggest that the effects of arsenic and influenza infection are additive such that mice that received both exposures had the worst outcome. These studies are ongoing and we now plan to identify the structural abnormalities in the lung associated with arsenic exposure. We will also use genetic data obtained from lung tissue in an attempt to identify arsenic sensitive pathways with a view to designing interventions that will prevent the progression of lung disease in affected communities.

Murine models of allergic airways inflammation.

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

Murine models have become increasingly popular over recent decades in order to elucidate the pathobiology of asthma. There are a number of variations in the methods for inducing allergic airways sensitisation in mice that involve systemic antigen sensitisation and subsequent antigen challenge of the airways. This work 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. In 2007 we were able to demonstrate 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 bronchoconstrictor 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 2007 and 2008 we followed up these studies in order to further elucidate the mechanisms of AHR. We conducted these studies in collaboration with Prof Holt, Dr Strickland, Dr Stumbles and Dr Wikstrom from the Division of Cell biology. 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 demonstrate that AHR required the presence of activated T cells in the airways. In subsequent experiments we studied the role of dendritic cells (DCs) and regulatory T cells (Tregs) in modulating AHR after repeated allergen exposure. 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 were able to show that suppression of AHR is linked to increased numbers of Tregs in the airway and altered antigen presentation by DCs. 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 to further elucidate the mechanisms of allergen induced AHR.

These studies are supported by the NHMRC

Response of Airways to Deep Inspiration in Health and Disease

Peter Noble, Graeme Zosky, Zoltan Hantos, Peter Sly

One of the most striking abnormalities in patients with obstructive lung disease is a loss of the bronchodilation that normally occurs in healthy individuals when they take a deep inspiration (DI). In both asthma and COPD, DI-induced bronchodilation fails. Studies undertaken in asthmatics indicate that the bronchial hyperresponsiveness and the DI phenotypes are closely linked, suggesting there may be shared mechanisms between the two. Explaining how DI-induced bronchodilation fails in obstructive lung

disease is critical to understanding how the pathology of these diseases leads to impaired lung function.

The above research area is the focus of two main research projects: (1) Investigation of DI responses in excised human airways. Lung tissue is obtained after lung resection surgery in cancer patients, and DI is simulated in airway segments using a motor controlled syringe pump and organ bath. The project aims to determine the intrinsic response of human airways to DI and establish whether these responses are modified in obstructive disease, including asthma and COPD. In 2009, 34 patients were recruited and tissue obtained from 22 subjects, while all recruited patients had additional lung function measurements performed in vivo. The project is NHMRC funded and will run for a further two years. It is expected that this project will generate novel and high impact data; (2) Investigation of DI responses in animal models. In order to better understand the mechanism(s) behind responses to DI, studies are currently underway to characterize DI responses in mouse airways in vivo and assess whether these responses are modified in a disease model (e.g., virus induced airway hyperresponsiveness). These experiments are supported by funding provided by a UWA Research Development Award, and will primarily be carried out by a newly recruited Honors student, Mr Russell Wong. Further, over the past few years, a series of comprehensive protocols have been carried out using excised animal airways (pig and sheep) to

examine DI responses in vitro resulting in numerous publications and providing the necessary preliminary data for our proposal to repeat these experiments using human airway tissue (see above). Several publications are pending using data from my own work, and earlier Honors student, Mr Elangovan Thaya Needi. In 2010, I will supervise a PhD student, Mr Thomas Ansell, who will carry on this work.

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

Alexander Larcombe, Elizabeth Bozanich, Rosa Gualano I, Gary Anderson I, Peter Sly, Debra Turner. (University of Melbourne)

This study investigates the mechanisms responsible for the increased airway responsiveness seen during infection with influenza (flu). 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 have provided a comprehensive assessment of the effects of acute influenza infection on lung function and airway responsiveness. The results have provided 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 flu using BALB/c, I29Sv and C57BL/6 mice. We were able to demonstrate that exposure to either virus, as an adult, results in acute airway hyperresponsiveness (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 (2007-2009).

In 2007 and 2008, we measured lung function, responses to methacholine (AHR) and inflammation in adult and weanling male and female BALB/c mice infected with influenza. 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. Furthermore, whereas adult mice infected as weanlings 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 and 2009 we began immunological analysis of dendritic and other antigen presenting cells harvested from BALB/c mice exposed to influenza and/or antigen in early life. These data are still being analysed.

We also extended the above experiments to investigate the effects of strain on responses to influenza infection. We replicated our mouse model of acute influenza infection in C57Bl/6 of various ages and found significant differences in BAL inflammatory kinetics between this strain and BALB/c mice. These data contribute significantly to our "Arsenic induced non-malignant lung disease" project and also show that the host defense factor of strain is vital in interpreting the effects of influenza infection on respiratory mechanics.

In 2009 we performed a series of experiments on influenza infected I29Sv mice, and neutrophil elastase (NE) knockout I29Sv mice. This mechanistic investigation was aimed at identifying whether a neutrophil serine protease

(NE), which has previously been associated with epithelial injury could be responsible for influenza induced AHR. We found that neutrophil elastase had no effect on cellular influx, cytokine production or AHR, with flu infected wild-type mice showing the same responses as NE knockouts.

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 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 bronchoalveolar lavage fluid (BALF) 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 BALF 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, in late 2008 and early 2009, 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 H₂O 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 performed additional lung function studies on mice exposed to tobacco smoke in utero. At 4 weeks of age, we found that these mice did not have impaired respiratory mechanics, nor did they show increased responsiveness to methacholine. These findings are important in that they suggest that impairment seen at 2 weeks of age may be completely recovered at 4 weeks of age in BALB/c mice.

We also measured urine cotinine levels of BALB/c dams to provide a 'real-world' comparison for our cigarette smoke exposure regime. These data show that our model of 6 cigarettes per day for 12 days during pregnancy is equivalent to a human mother smoking approximately 20-40 cigarettes per day during the same period.

Development and characterization of a mouse model of acute diesel exhaust particle exposure.

In humans, recent epidemiological evidence has shown an increase in the prevalence of various allergic respiratory diseases, including asthma, in many developed

countries. This increase has paralleled a worldwide escalation in the use of fossil fuels, such as diesel. These data suggest a link between exposure to fossil fuel products and exacerbation of existing respiratory illness. This project is designed to create and characterize a mouse model of diesel exhaust particle (DEP) exposure, in addition to investigating the effects of acute DEP exposure on exacerbations of existing airway/lung diseases such as asthma and influenza.

In 2009 we developed and characterized the mouse model of DEP exposure. Adult BALB/c mice were inoculated intranasally with either 10, 30 or 100µg DEP in saline and TWEEN-80. At various time points (3, 6, 12, 24, 48 hours, and 7, 14, 28 days) after inoculation, mice BAL samples were taken from male and female mice for analysis of inflammation (total and differential cell counts), cytokine/chemokine influx and uptake of carbon black by alveolar macrophages (AM). We found that these parameters were heavily influenced by dose and time. The peak of inflammation was measured 6 hours after inoculation in mice dosed with 100µg of DEP. This peak was associated with commensurate peaks in cytokines such as MCP-1 and MIP-2, and uptake of carbon black by AM. Mice inoculated with 10 or 30µg diesel did not show detectable inflammation.

We also measured lung function in adult male and female mice inoculated with 100µg DEP, at 6 and 24 hours after exposure. We found significant impairments in tissue elastance and tissue damping in

mice 6 hours after exposure, which had completely recovered by 24 hours. There were no effects of DEP exposure on airway resistance.

In 2010 we aim to expand on these findings by investigating the effects of an acute exposure to DEP on existing allergic airways disease, and in mice with existing respiratory viral infections. We also aim to extend these studies into looking at the effects of biodiesel exposure on lung function, in addition to establishing a chronic model of DEP exposure.

Clinical Asthma Studies

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

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

263 children at high risk of atopy were recruited into this prospective birth cohort between 1996-1998. Close follow-up occurred in the first 5 years with extensive data collection on early respiratory infections and the development of atopy and allergic diseases including eczema and asthma, as well as wheeze. Significant associations between rhinovirus and RSV-induced wheezy lower respiratory infections in the first year of life and the subsequent development of persistent wheeze at 5 years have been reported.

The 10 year follow-up visit was completed

in August 2008. At this follow-up, blood tests for immune function and development, skin prick tests and lung function tests were performed. Data on environmental exposures since the last follow-up visit at 5 years was also collected. Data from this cohort will provide important information on the role of early life factors, in particular the role of respiratory viruses, in immune development and maturation. It will enhance our understanding of the interaction of early life factors in the pathogenesis of wheeze and asthma phenotypes that persist beyond early childhood. The ongoing support and commitment of the study children and their families is acknowledged.

Cystic Fibrosis

Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening

Peter Sly, Siobhain Brennan, Catherine Gangell, Nick deKlerk, Conor Murray, Lauren Mott and Stephen Stick

The promise of newborn screening (NBS) for cystic fibrosis (CF) has not been fully realized, and the extent of improvement in respiratory outcomes is unclear. We hypothesized that significant lung disease was present at diagnosis.

To determine the extent of lung disease in a geographically defined population of infants with CF diagnosed after detection

by NBS.

Fifty-seven infants (median age, 3.6 mo) with CF underwent bronchoalveolar lavage and chest computed tomography (CT) using a three-slice inspiratory and expiratory protocol.

Despite the absence of respiratory symptoms in 48 (84.2%) of infants, a substantial proportion had lung disease with bacterial infection detected in 12 (21.1%), including *Staphylococcus aureus* (n=4) and *Pseudomonas aeruginosa* (n=3); neutrophilic inflammation (41.4×10³ cells/ml, representing 18.7% of total cell count); proinflammatory cytokines, with 44 (77.2%) having detectable IL-8; and 17 (29.8%) having detectable free neutrophil elastase activity. Inflammation was increased in those with infection and respiratory symptoms; however, the majority of those infected were asymptomatic

Radiologic evidence of structural lung disease was common, with 46 (80.7%) having an abnormal CT; 11 (18.6%) had bronchial dilatation, 27 (45.0%) had bronchial wall thickening, and 40 (66.7%) had gas trapping. On multivariate analysis, free neutrophil elastase activity was associated with structural lung disease. Most children with structural lung disease had no clinically apparent lung disease.

These data support the need for full evaluation in infancy and argue for new treatment strategies, especially those targeting neutrophilic inflammation, if the promise of NBS for CF is to be realized.

American Journal of Respiratory and Critical Care Medicine; 2009, 180:146–152

Bronchiectasis in an asymptomatic infant with cystic fibrosis diagnosed following newborn screening

Lauren Mott, Catherine Gangell, Conor Murray, Stephen Stick, Peter Sly

Many countries have introduced newborn screening for cystic fibrosis to facilitate diagnosis prior to the development of lung disease. Although most infants with cystic fibrosis are asymptomatic from a respiratory point of view at diagnosis, structural lung disease has been detected by computed tomography. We present a case of an asymptomatic infant with cystic fibrosis diagnosed following newborn screening who had endobronchial infection with *Pseudomonas aeruginosa* and radiological evidence of bronchiectasis at 3 months of age.

Journal of Cystic Fibrosis; 2009, 8:285–287

Alveolar macrophages and CC chemokines are increased in children with cystic fibrosis

Siobhain Brennan, Peter Sly, Catherine Gangell, Nina Sturges, Kaye Winfield, Matt Wikstrom, Samantha Gard, John Upham

Airway inflammation is an important component of cystic fibrosis (CF) lung disease. We sought to determine whether alveolar macrophages (AM) were involved in early CF lung disease.

Children with CF (median age 3.1 yrs) participated in a surveillance program that included annual bronchoalveolar lavage (BAL). Control samples were obtained from non-CF children (median age 3.1 yrs; n=24) investigated for persistent respiratory symptoms.

Pulmonary infection was detected in 31% (16/51) and 38% (9/24) of children from the CF and non-CF groups respectively. AM in BAL were increased in CF compared with non-CF in the absence of infection (223 vs. 85 ×10³ cells/mL; p=0.001) and were associated with elevations in the CC chemokines MIP3 (CCL20; 355.8 vs. 46.0 pg/mL-I; p<0.001), MCP-1 (CCL2; 263.5 vs. 25.3pg/mL-I; ;p<0.001), MIP-1 (CCL-3; 38.2 vs. 4.9 pg mL-I; p<0.001), & MIP-1 (CCL4;326.6 vs. 27.5 pg/mL-I; p<0.001) Total cell counts and neutrophil numbers increased in the presence of infection however, there was no additional effect of CF.

Alveolar macrophages and CC chemokines are elevated in the lungs in young children with CF even in the absence of pulmonary infection. Longitudinal studies will be required to determine the clinical relevance of these findings.

European Respiratory Journal; 2009, 34:655-61

Bronchiectasis in Infants and Preschool Children Diagnosed with Cystic Fibrosis after Newborn Screening

Stephen Stick, Siobhain Brennan, Conor Murray, Tonia Douglas, Britta S. von Ungern-Sternberg, Luke Garratt, Catherine Gangell, Nicholas De Klerk, Peter Sly

The objectives of this study were to determine the prevalence of bronchiectasis in young children with cystic fibrosis (CF) diagnosed after newborn screening (NBS) and the relationship of bronchiectasis to pulmonary inflammation and infection.

Children were diagnosed with CF after NBS. Computed tomography and bronchoalveolar lavage were performed with anesthesia (n=96). Scans were analysed for the presence and extent of abnormalities.

Results The prevalence of bronchiectasis was 22% and increased with age (p=0.001). Factors associated with bronchiectasis included absolute neutrophil count (p=0.03), neutrophil elastase concentration (p=0.001), and *Pseudomonas aeruginosa* infection (p=0.03).

Conclusions Pulmonary abnormalities are common in infants and young children with CF and relate to neutrophilic inflammation and infection with *P. aeruginosa*. Current models of care for infants with CF fail to prevent respiratory sequelae. Bronchiectasis is a clinically relevant endpoint that could be used for intervention trials that commence soon after CF is diagnosed after NBS.

Journal of Pediatrics; 2009, 155:623-628

Children's Environmental Health

Kwinana Children's Respiratory Health Study

Peter Sly, Peter Franklin, Tania Gavidia and Merci Kusel

For many years there has been community concern about the potential health effects of air pollution in the Kwinana electoral district, where industry and community co-exist. In response to these concerns, the Department of Health (WA) commissioned a respiratory health study to assess the air pollution and respiratory health of children around Kwinana Industrial Area (KIA).

The study was carried out in June 2009. A health and environment questionnaire was used to collect respiratory history and environmental data for almost 591 children. Using lung function (Forced Oscillation Technique and Spirometry) techniques and Skin Prick Tests, the study team collected respiratory and allergy data for 510 children. The Department of Environment and Conservation has been monitoring the air quality around the area since the commencement of the study for a period of 12 months (June 2009 - June 2010). A 6-month follow up health and housing questionnaire was sent to parents in February 2010. All children (aged 5 to 12 years) were recruited from 10 primary schools in the Kwinana area. Parental

consent was needed for all children to be included in the study.

We are currently awaiting the return of the 6-month Follow-up Questionnaire and have begun analysis of the data collected in June 2009. The analysis will compare the lung function results and housing and environment data with other children in Perth (Caversham, Duncraig Perth CBD and Swanbourne), who were tested in as part of the Australian Child Health and Air Pollution Study (ACHAPS).

The results of the Kwinana Childhood Respiratory Health Study will address the following questions:

- Do children in Kwinana have more respiratory (breathing) problems than children in other parts of Perth?
- Are children in Kwinana exposed to worse air quality than children in other parts of Perth?
- Is there any evidence that Kwinana air causes respiratory (breathing) problems for children living in the area?

WHO III International Conference on Children's Environmental Health: Emerging Issues: From Research and Policy to Action. 7- 10 June, 2009.

Peter Sly and Tania Gavidia

The Third WHO International Conference on Children's Health and the Environment was held in Busan, Republic of Korea from 7-10 June 2009, hosted by the Ministry of Environment in the Republic of Korea

and organized by WHO Headquarters and WHO Collaborating Centre for Children's Environmental Health, Perth, WA.

The conference was provided a unique international forum for discussing critical issues to children's health and their environment, and addressed current and emerging trends, new scientific research findings, and the translation of research to policy to protect the children's health from known environmental threats.

The WHO Collaborating Centre for Children's Environmental Health provided important in-kind contribution and was fundamental in the planning and execution of the event.

Guangxi-Australia Joint workshop on Children's Environmental Health and Neurodevelopment. 26 – 27th April, 2009.

Peter Sly, Merci Kusel, Bee-Hong Lo, Tania Gavidia

Dachang is a small mining town in Guangxi Zhuang Autonomous Region in Southern China, housing many minority populations. The dust resulting from the heavy traffic, mainly the vehicles transporting the ore, causes a serious amount of suspended particle pollution in the air, much of which is deposited the ground in the surrounding area. The inhabitants have to wear masks when walking outside. Cultivation of food and animals for consumption is also carried out by many of the inhabitants, thus resulting in human

exposure to pollutants through inhalation, ingestion, and dermal exposure. The WHO Collaborating Centre conducted a 2 day workshop (26-27th April 2009) in Nanning, Province of Guangxi with the aim of training environmental scientists and medical doctors on how to appropriately measure lung function using spirometric testing and carry out neurodevelopmental assessments.

CEH Survey for Health Professionals

Peter Sly, Leith Sly and Tania Gavidia

A number of childhood diseases are linked to unsafe and degraded environments. However, many health care providers (HCP) are unable to recognise, assess and manage environmentally-related diseases in children. To obtain a better understanding of the awareness and knowledge that health professionals possess on environmental issues that may pose threats to children's health, the WHO Collaborating Centre for Children's Environmental Health (CEH) has conducted surveys amongst members of different national and international paediatric, respiratory and environmental professional associations.

Members of different professional associations were invited to participate through a web based questionnaire enquiring into the extent of their awareness of issues in children's environmental health. The results of the surveys have been presented at national (TSANZ 2009, Darwin, Australia) and

international (ERS 2009, Vienna, Austria) conferences.

Graduate Certificate on CEH, Curtin University

Peter Sly and Leith Sly

One of the aims of the WHO Collaborating Centre is to provide access to high quality education and training, as currently there is a lack of courses specifically designed to provide training and qualifications in Children's Environmental Health. The Centre sees improvement of training opportunities in Children's Environmental Health as a high priority and has undertaken a program of developing training modules for this purpose.

Curtin University of Technology, in collaboration with the WHO Collaborating Centre for Research on Children's Environmental Health, offer a Graduate Certificate in Children's Environmental Health (<http://www.ichr.uwa.edu.au/files/user26/CEHcurtinbrochure.pdf>). The course provides a specialist program in understanding children's special vulnerability to environmental exposures and their adverse health outcomes.

The course can be studied full time or part time and is designed to be a fully online course, facilitating access to international and local students. The Graduate Certificate on Children's Environmental Health has been accredited by the European Board for Accreditation (EBA)

in Pneumology and students successfully completing the course will receive 184 CME credits.

Healthy Environments for Children Alliance (HECA) Newsletter

Kathryn Ramsey and Tania Gavidia

Since September 2009, the WHO Collaborating Centre is responsible for compiling and editing HECANet a WHO/ UNEP joint initiative to distribute children's environmental health related information to relevant stakeholders and interested individuals. The newsletter is distributed to over 2500 subscribers every month (more information available from <http://www.who.int/heca/infomaterials/hecanet/en/index.html>).

Clinical Respiratory Physiology

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

Study Team: Prof. Peter Sly, Prof Stephen Stick, Karla Logie, Maureen Verheggen, Dr Andrew Wilson, Claire Shackelton and Dr Catherine Gangell.

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

clinical respiratory physiology is a major study outcome. These are summarised below

Lung function outcomes in infants and preschool diagnosed with Cystic Fibrosis

Graham Hall, Catherine Gangell, Karla Logie, Sarath Ranganathan (Royal Children's Hospital, Melbourne), Stephen M Stick and Peter D. Sly for the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF)

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

are being compared to bronchoscopies, bronchial alveolar lavage and computed tomography scans as well as blood, genetics and urine sampling.

These studies are supported by the USA CF Foundation and NHMRC. For full details please see Cystic Fibrosis research area summary.

Investigation of the influence preterm birth on lung structure and function in school age children

Graham Hall, Andrew Wilson (Respiratory, PMH), Jane Pillow (KEMH), Andrew Maiorana (RPH, Curtin University) and Karla Logie.

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of premature birth. Indeed BPD is the most common form of chronic lung disease in infancy. There has been a gradual but significant change in the pathogenesis, epidemiology and clinical syndrome of BPD. The two major factors influencing this change are the improvements in neonatal respiratory care, and consequently the dramatically improved survival of children born extremely preterm. The most common clinical picture is now so different to Northway's original description that the term "New BPD" is used to describe the contemporary disease.

In 2009 we obtained pilot data on the pulmonary structural and functional consequences of BPD in a group of 9 to 11 year children with a history of BPD

following preterm birth. We studied 30 children with BPD and 28 healthy controls and obtained chest CT scans in 26 children with BPD and assessments of partitioned DLCO in 23 children with BPD and 28 healthy controls. In addition we have assessments of FOT, spirometry, lung volumes and cardiopulmonary exercise tests. Thus far we have obtained all attempted measurements (including CPET) in >80% of children.

Nearly all children with BPD had abnormal chest CT with hyperlucent areas, multifocal architectural distortion and radial linear densities being the most common abnormalities noted. Since commencing measurements of partitioned DLCO, acceptable and repeatable measurements have been obtained in 80% of children. These feasibility data demonstrate 9-11 year old children with BPD are able to achieve acceptable and repeatable measurements across the range of tests being proposed.

Identification of optimal spacer selection for delivery of salbutamol to asthmatic children

Graham Hall, Sunalene Devadason (SPACH, UWA), Claire Shackelton (Respiratory, PMH) and Kevin Looi (SPACH, UWA)

The method of delivery for asthma medications significantly impacts on the clinical outcomes in terms of the assessment of bronchodilator responsiveness for lung function testing and the time spent in emergency

departments. In children spacers are the preferred option for medication delivery. Spacer performance can vary significantly and may depend on spacer size, construction design and materials and inhalation methods. This project has two distinct stages

Stage 1: We will record breathing patterns from children ages 3-18 years and then use these patterns to measure the amount of salbutamol (Ventolin) that various commercially available spacers deliver using a flow volume simulator.

Stage 2a: Using the information from stage 1 we will test lung function before and after salbutamol inhalation using the spacer that gives the highest delivered dose and the most cost effective spacer (taking into account purchase and sterilisation costs).

Stage 2b: Using the information from stage 1 we will assess if children admitted to PMH for an acute asthma exacerbation are admitted for longer when using the spacer providing the best cost effectiveness when compared to the spacer with the highest salbutamol delivery.

To date we have recorded breathing patterns in 16 children aged between 3 and 18 using both tidal breathing and a slow maximal breath in to total lung capacity. Using these breathing patterns we then assessed the amount of salbutamol each spacer delivered with the flow-volume simulator. From these simulations we determined that the Space Pod spacer delivered the highest dose of salbutamol

across all age group using both breathing types. In terms of cost effective spacers the Lite Aire performed best for slow, maximal inhalations (used for lung function testing) while the E-Chamber performed best using tidal breathing (used for PMH admissions). Stages 2a and 2b are currently underway

Characterising objective lung function measures in young children with recurrent wheeze

Study Team: Graham Hall, Andrew Wilson (Respiratory, PMH), Afaf Albloushi.

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

This study aims to investigate the influence of respiratory history and symptoms on

lung function and bronchodilator

Staff and Students

Head of Division

Peter D Sly MD MBBS DSc FRACP

Research Staff

Carlie Dunford BSc

K.E (Bill) Finucane (Emeritus Professor)

Felicity S Flack PhD

Rachel Foong BSc(Hons)

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

Ingrid Laing PhD

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

Peter Noble PhD

Faith Parsons

Leith Sly PhD

Debra J Turner PhD (Program Coordinator

of Respiratory Physiology Research,
Adjunct Senior Lecturer UWA)

Britta von Ungern Sternberg,
(Occupational Trainee, Consultant
Anaesthetist, PMH)

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

Research Support

Luke Berry BSc – Laboratory Manager

Cameron Brooke

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Postgraduate Students

Angela Alessandri MBBS FRACP (Paeds),
MBioeth PhD Candidate

Liz Bozanich PhD Candidate

Lauren Mott MBBS PhD Candidate

Kathryn Ramsey BSc(Hons) PhD Candidate

Vincenzo Canizzarro MD

Students

Catherine Boylen – Honours

Michael Stutz - Honours

Theses passed

Tonia Douglas MD, University of
Manchester

Vincenzo Cannizzaro PhD, University of
Szeged

Britta von Ungern-Sternberg PhD,
University of Szeged

Sylvana Bettiol, MPH, Curtin University

Awards

Graeme Zosky Occupational and
Environmental Lung Disease Best
Presentation TSANZ ASM

Graeme Zosky Maurice Blackburn Lawyers
International Travel Award

Kathryn Ramsey U.W.A. Convocation
Travel Award

Peter Noble 2009 Raine Research Prize

Alexander Larcombe Thoracic Society
of Australia and New Zealand (TSANZ)
Travel Award 2009

Alexander Larcombe Lung Institute of
Western Australia Senior Medical Scientist
Award 2009

External Committees

International

Peter Sly Pacific Basin Consortium on
Environment and Health. Board Member
(2005-, Chairman of Board (2007-)

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

Scientific Advisory Committee (2003 -).

Peter Sly World Health Organization
Long-term Children's Study Advisory
Group (2005-).

Peter Sly Global Initiative for Asthma
(GINA) Pediatric Working Group (2008-).

Peter Sly Canadian Healthy Infant
Longitudinal Development (CHILD) Study,
Canada (2005 -).

Peter Sly Infant Lung Health Study, Paarl,
South Africa (2008-).

Peter Sly A Phase II/III multicentre,
controlled, double-blind study using
immunoprophylaxis in the primary
prevention of asthma; ITN025AD, BB-
IND# 12940, (2004-).

Peter Sly Pediatric Organization for
Worldwide Respiratory Research
(POWRR) (2005-).

Peter Sly Asian Pacific Association
of Pediatric Allergy Respiratory and
Immunology, Executive Member (2008 -).

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)

Merci Kusel Editorial Board member,
Paediatrics and Child Health in General
Practice journal

Regional

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

Peter Sly Telethon Institute for Child Health Research Executive Committee

Peter Sly Asthma Foundation of Western Australia Medical Advisory Committee

Debra Turner Board of Directors, Scitech, Western Australia

Local

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

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

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

Invited Presentations

Peter Noble 'The Dynamic Breathing Environment – regulation of airway narrowing and evolution of airway hyperresponsiveness'. Thoracic Society of Australia & New Zealand, WA Branch, Mandurah, 18/10/2009.

Peter Sly Windows of development: respiratory and immune systems. Third International WHO Conference on

Children's Health and the Environment. Busan, Korea. June 2009.

Peter Sly Diagnosis of early lung disease in CF. 12th Brazilian Congresso of Pediatric Pneumology. São Paulo, Brazil. June 2009

Peter Sly Recurrent Wheezing in Preschool Children. 12th Brazilian Congresso of Pediatric Pneumology. São Paulo, Brazil. June 2009

Peter Sly Environmental Pollution and Respiratory Disease in Children. 12th Brazilian Congresso of Pediatric Pneumology. São Paulo, Brazil. June 2009

Peter Sly Early Pseudomonas infection in CF. 12th Brazilian Congresso of Pediatric Pneumology. São Paulo, Brazil. June 2009.

Peter Sly Recurrent Wheezing in Preschool Children. PMG Advancing Paediatrics Weekend. South Africa. July 2009

Peter Sly Environmental Pollution and Respiratory Disease in Children. PMG Advancing Paediatrics Weekend. South Africa. July 2009

Peter Sly Paediatric Spirometry; how, when & why. PMG Advancing Paediatrics Weekend. South Africa. July 2009

Peter Sly The role of DNA methylation in Th1/Th2 differentiation. European Respiratory Society. Austria, September 2009

Peter Sly In utero exposures. European Respiratory Society. Austria, September 2009

Peter Sly The next steps in air pollution research in children. American Thoracic Society International Conference. San Diego, USA, May 2009.

Peter Sly Nanotechnology and Manufactured Nanoparticles – Are They important for Children's Environmental Health? Third International WHO Conference on Children's Health and the Environment. Busan, Korea, June 2009

Peter Sly Neutrophilic inflammation predisposes to structural lung disease in cystic fibrosis (CF) via neutrophil elastase activity. European Respiratory Society, September 2009

Peter Sly Nanotechnology and Manufactured Nanoparticles – Are they important for Children's Environmental Health? 13th International Conference of the Pacific Basin Consortium, Australia, November 2009

Peter Sly Environmental Health Issues and Vulnerable Groups in Latin America. Do we need a new Agenda? 13th International Conference of the Pacific Basin Consortium, Australia, November 2009

Peter Sly Introduction on Environmental Health. Nanning, China, April 2009.

Peter Sly Spirometers and technique for performing spirometry and contraindications. Nanning, China, April 2009.

Peter Sly Interpreting the results (Spirometry): what do these tell you? Nanning, China, April 2009.

Peter Sly Outdoor Air Pollution. Third International WHO Conference on Children's Health and the Environment. Busan, Korea. June 2009

Peter Sly Infant Lung Function Workshop. PMG Advancing Paediatrics Weekend. South Africa. July 2009

Peter Sly Susceptibility of children to environmental pollutants. 13th International Conference of the Pacific Basin Consortium, Australia, November 2009

Peter Sly Vulnerability of Children to Air Pollution. 13th International Conference of the Pacific Basin Consortium, Australia, November 2009

Peter Sly Environmental impacts on prenatal lung development: Out of sight but not out of mind. Australian and New Zealand Society of Respiratory Science. Perth, October 2009.

Funding

Alexander Larcombe UWA Research Development Awards 2010 - \$14,805 - Rhinovirus Infection Results in Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) Symptoms in a Mouse Model of COPD.

Internal collaborations

Active collaborations exist with:

- Pat Holt and the Cell Biology group
- Wayne Thomas
- Prue Hart and Shelley Gorman
- Nick de Klerk
- Stephen Zubrick

Alexander Larcombe

- Airway mucosal DC maturation is controlled by local T cell interactions following repeated antigen challenge (with Deborah Strickland and Patrick Holt, Division of Cell Biology)
- Characterisation of mouse respiratory tract antigen presenting cell and dendritic cell populations and their response during allergic airway inflammation and early life viral infection (Phil Stumbles, Division of Cell Biology)
- Potential to boost airway mucosal T regulatory cell number and function, in a rat model of OVA induced experimental allergic airways inflammation, by oral administration of OM Pharma-85 (with Deborah Strickland and Patrick Holt, Division of Cell Biology)

External Collaborations:

Genetics of Asthma Investigators Network (GAIN). Peter Helms (Aberdeen, UK),

Michael Silverman (Leicester, UK), Karin Lodrup-Carlsen (Oslo, Norway); Moira Whyte (Sheffield, UK); Warren Lenny (Stoke on Trent, UK); John Tsanakas, (Thessaloniki, Greece); Jorrit Gerritsen (Groningen, Netherlands); Andrea von Berg (Wesel, Germany); Kathleen Barnes (Baltimore, USA); John Sundry (Durham, USA).

This collaboration, formed in conjunction with Glaxo SmithKline, conducted a large international study investigating the genetics of asthma through genome scanning. Over 1100 family consisting of both biological parents and at least two asthmatic children were recruited. The network is still active and meets regularly. Publications arising from this collaboration appear in my publication list as Refereed journal articles numbers: 207; 229; 244; 266; 275.

Additional publications arising from this collaboration are;

- Zhu,G.; Whyte,M.K.; Vestbo,J.; Carlsen,K.; Carlsen,K.H.; Lenney,W.; Silverman,M.; Helms,P.; Pillai,S.G. Interleukin 18 receptor 1 gene polymorphisms are associated with asthma. *Eur J Human Genetics* 2008;9:23-29.
- Zhu,G.Vestbo,J. Lenney,W. Silverman,M. Whyte,M. Helms,P. Anderson,W.H. Pillai,S.G. Association of PTGDR gene polymorphisms with asthma in two Caucasian populations. *Genes Immun* 2007;8:398-403.
- Munthe-Kaas,M.C.; Carlsen,K.H.; Helms,P.J.; Gerritsen,J.; Whyte,M.;

Feijen,M.; Skinningsrud,B.; Main,M.; Kwong,G.N.; Lie,B.A.; Lodrup Carlsen,K.C.; Undlien,D.E. CTLA-4 polymorphisms in allergy and asthma and the TH1/TH2 paradigm. *J Allergy Clin. Immunol.* 2004;114:280-7.

Professor Zoltan Hantos, University of Szeged, Hungary.

Zoltan Hantos is an engineer with an international reputation in respiratory physiology, especially the engineering aspects, and in computer modelling. He developed non-invasive methods for partitioning lung function into components representing airway and lung tissue through the measurement of respiratory impedance at low-frequencies and the application of a computer model. Collaboration with Zoltan was established when the group wanted to develop methods for measuring lung tissue mechanics non-invasively in infants and our collaboration continues. We share responsibility for study ideas and study design, he supplies the engineering and modelling expertise and we supply the expertise in measuring lung function in infants. We also collaborate on studies measuring airway and lung tissue mechanics in small animals and in developing new methods for measuring lung function in all age groups using broad-band forced oscillations. He has jointly supervised several PhD students enrolled at UWA (Graham Hall, Jane Pillow, Rachel Collins, Cindy Thamrin) or at the University of Szeged (Feri Petak, Walid Habre, Tibor Janosi, Vincenzo Cannizarro). Zoltan has

been a co-investigator on NHMRC grants #139024, #404141.

Professor Janet Stocks, Institute for Child Health, London

The collaboration with Janet Stocks has evolved from her initiative to establish truly International collaboration to produce standards for measuring lung function in Infants. Janet approached a group of investigators active in the field of infant lung function testing, including me, in the late 1980's and formed a working group that became the first committee for any purpose to be jointly ratified by the American Thoracic Society and European Respiratory Society. This group has since achieved Task Force status. I have been a member of this group since its inception and was Chairman of the European Section from 1994 to 1996. This group continues to be extremely active, meeting twice a year coinciding with the annual scientific meetings of the two societies, and is currently working with Industry to produce acceptable standards for the building of equipment and to produce standard software for performing and analysing tests of infant lung function. These steps are critical to being able to compare data between centres, to perform multi-centre collaborative studies and to advance measurements of infant lung function. The group have produced a text book (BI) and a number of consensus and standards documents.

Dr Walid Habre, Children's Hospital,

Geneva, Switzerland, Dr. Ferenk Petak, University of Szeged, Hungary

The collaboration with Walid Habre began when he spent two years in the Department of Anaesthesia, Princess Margaret Hospital, Perth. He was interested in investigating the effects of new anaesthetic agents on lung function on children, particularly those with asthma. Together, we planned and conducted a number of studies with anaesthetic agents, measuring lung function during mechanical ventilation both in animal models and in children. Peter Sly supervised his PhD in conjunction with Zoltan Hantos. Dr. Ferenk Petak was also a PhD student within Clinical Sciences; some of his studies were performed in Perth and some in Szeged, with Zoltan Hantos. Dr. Petak now collaborates with Walid Habre, travelling regularly from Szeged to Geneva. Both Zoltan Hantos and Peter Sly have been co-applicants on 5 successful grants from the Swiss National Research Foundation.

Dr Isabelle Romieu, Instituto Nacional de Salud Publica, Cuernavaca, Mexico.

Peter Sly has begun a new collaboration with Dr. Romieu recently. He has worked with Isabelle on committees within the American Thoracic Society and in 2006-7 spent a three month mini sabbatical in her lab in Cuernavaca. This collaboration forms part of the activities with the WHO Collaborating Centre for Research on Children's Environmental Health. Peter Sly and Graham Hall are

advising on the respiratory follow-up of a prenatal intervention trial of nutritional supplementation. We have established lung function testing for preschool aged children in Mexico for this study, which has received funding from the USA NIH.

Dr. Enrico Lombardi, Ana Meyer Ospedale Pediatrico, Firenze, Italy

Peter Sly has acted as a mentor for Dr. Lombardi through his training and is now actively collaborating on projects related to measuring lung function in preschool aged children. Dr. Claudia Calogero completed her respiratory training within Clinical Sciences and now works with Enrico in Florence.

Dr. Renato Stein, Porto Alegre, Brazil

Peter Sly has acted as a scientific mentor and collaborator for Dr. Renato Stein, especially in the area of environmental influences on childhood asthma. In addition, one of his staff (Dr. Paulo Pitrez) trained within Clinical Sciences.

Diabetes Research Group

Overview

Our general research interest is in clinical investigation in metabolism and endocrinology with a focus on the young. More specific areas of research have been in diabetes and obesity. We have a particular focus on insulin therapy in diabetes, acute and chronic diabetes complications particularly hypoglycaemia. The techniques employed have included epidemiological analyses of longitudinal and cross sectional datasets, descriptive investigations, hypothesis guided clinical experiments and clinical trials.

We have established prospective monitoring of a population based sample of children and adolescents with Type 1, Type 2 Diabetes and Obesity and this has led to several key publications. It has also generated questions of relevance to diabetes management and directions of investigation that we have addressed directly with specific protocols. Collaboration with experts in relevant fields has been critical. In addition we have developed a key resource including DNA and serum banks that can be employed in future investigations given the close phenotype that has been documented. We have established several trials including exercise programs in Type 1 diabetes and obesity, intensive insulin therapy from diagnosis of diabetes, use of statins and ace inhibition in preventing microvascular and macrovascular complications in Type 1 diabetes and novel therapies for severe obesity.

Epidemiology

Western Australian Children's Diabetes Database

The aim of this register is to provide a population-based register of all children and adolescents resident in WA who are diagnosed with diabetes before the age of 16y, in order to study the epidemiology of Type 1 diabetes in the state. Since 2006 the database has been updated to hold family history data of the child with diabetes's immediately blood relatives – including half-siblings. The register may also prove helpful in exploring the, as yet, undefined aetiology of Type 1 diabetes (T1D). It also facilitates future studies requiring the identification of family members at risk of diabetes, who may be eligible for participation in clinical trials for disease prevention.

The project has been able to establish incidence data on newly diagnosed insulin treated diabetes patients aged less than 15 years at age of diagnosis, and childhood-onset type 2 diabetes (T2D). It has also enabled cohort studies on severe hypoglycaemic events over time, and the impact of pump therapy on diabetes management.

T1D & T2D DNA banks

TW Jones, EA Davis

The aim of this study is to create a statewide DNA bank in conjunction with the Western Australian Institute for Medical Research. This dual site DNA bank

will hold DNA samples from all T1D and T2D patients who attend any of the PMH diabetes clinics in WA, and their biological families. The bank has been established as a valuable resource for research into the genetics of Type 1 and Type 2 Diabetes and its complications, and other related autoimmune diseases.

2252 subjects have had DNA stored so far. Using this resource we have investigated the role of the ACE gene in the development of renal disease and also in severe hypoglycaemia, in previous years.

Funding: NHMRC Enabling Grant;

Longitudinal Type 1 and Type 2 Diabetes Serum Repository (LDSR)

TW Jones, EA Davis

The primary aim is to establish and maintain a serum repository to enable proteomic research. We hypothesise that Type 1 and type 2 diabetic children's serum will contain biomarkers for complications and as T1D and T2D has a strong genetic contribution the children's biological parents' serum should also contain biomarkers to help us to identify proteins of interest

All Type 1 and Type 2 Diabetes patients seen by the endocrinologists at Princess Margaret Hospital, inclusive of both current and ex-patients and their biological parents will be asked to participate.

Currently 2 studies have accessed samples from this repository (final analysis pending) – investigating the biomarkers of the

risk of developing microalbuminuria & macroalbuminuria in adolescents with T1D, and the risk of severe hypoglycaemia events.

To date the repository holds 850 samples.

Funding: NHMRC Enabling Grant

Australian Childhood Diabetes DNA Repository

T.W Jones, E.A Davis, G. Morahan, F. Christiansen (W.A Investigators)

To identify and recruit 3000 families across Australia affected by either type 1 or young onset type 2 diabetes mellitus (T1D or cT2D); to develop and maintain a database and Repository of DNA samples from these families. All children diagnosed with Type 1 diabetes between the age of 1 and 35 years, or young onset type 2 between the age of 1 and 18 years; and with both biological parents (family trio) willing to participate, are recruited. Salivary samples are collected from the child and both parents, for DNA extraction and are asked to answer a short medical history questionnaire.

To date we have 302 completed family trios, and 78 incomplete families where a sample is needed from one member of the trio.

Funding Source: NHMRC enabling grant

A database of the complications of obesity in children

E.A Davis, L. Bell

The aim of this study is to identify the features and the medical complications of children with obesity in WA who present to a public hospital. A database has been set up and maintained to store this information. This data will be used to identify the prevalence of medical and psychological complications, and to track changes over time with changes in BMI z score. The study population is overweight and obese children who see specialist paediatricians in WA for treatment of their weight problem. Data collection commenced in March 2004. There are currently 168 overweight or obese subjects with data recorded on the database.

A datasheet derived has been developed for use in the clinical setting. Prevalence rates for the medical and psychological complications of obesity have been generated from examination findings and investigations. Since 2007, the findings from this study have been published in 7 refereed journal articles and presented for 2 invited addresses, 4 international conferences and 6 national conferences

Funding: internal

Western Australian DNA database and longitudinal serum storage for study of childhood weight regulation

E.A Davis, T.W Jones, S Byrne, J.A Curran

The purpose of this bank is to be a resource for studies into childhood weight regulation disorders in Western Australia

– for example heart disease, joint diseases and type 2 diabetes which occur more commonly in overweight/obese individuals than healthy weight individuals. This ongoing longitudinal study will develop a collection of DNA and blood samples from overweight and obese children, lean controls and their parents.

The individuals that will be eligible for recruitment to the study will be overweight children seen for their weight problem at Princess Margaret hospital, their siblings and parents, and families enrolled in the Growth and Development study through the Institute of Child Health Research. To date, 830 DNA samples and 209 serum samples have been stored to date. A study investigating biomarkers of obesity has accessed samples from this repository (final analysis pending).

Funding: Department of Endocrinology and Diabetes, PMH, Endocrine Research Fund; NHMRC Enabling Grant

Factors affecting the development and persistence of childhood obesity: Growth and Development Study

S Byrne, EA Davis, E Geelhoed, E Blair, S Zubrick

This is a prospective cohort study involving three groups of children aged 6-12 years, and is a collaborative study with the School of Psychology UWA. The cohort includes a clinical sample of 100 obese children attending the PMH Obesity Clinic, a community sample of 360 overweight or

obese children, and a community sample of 360 healthy weight children recruited from metropolitan primary schools, and their parent(s). Exclusion criteria: obesity due to a specific known medical condition; presence of a medical condition that affects body weight; neither parent agrees to participate; or non-English speaking.

The main aim of this study is to identify factors that predict the development and persistence of childhood obesity. Children and their parent(s) will be assessed upon enrolment into the study and then followed-up bi-annually for at least three years.

Funding Source: Healthway Project grant

Fremantle Diabetes Study Phase II

EA Davis, TME Davis, DG Bruce, WA Davis, E Geelhoed, MW Knuiman, SP Chubb

The aims of the Fremantle Diabetes Study (Phase II) are as follows:

1. To build on the original (Phase I) Fremantle Diabetes Study (FDS) by recruiting all consenting diabetic patients in the same catchment area in order to perform a detailed comparison of prevalence, care, control and complications in 2008-2012 to those in 1993-2001.
2. To provide novel long-term data on survivors with type 1, type 2 or latent autoimmune diabetes of adults (LADA) from Phase I, especially in relation to i) risk factors for, and progression of, micro- and macroangiopathy, ii) important non-

standard complications identified through Phase I such as osteoporosis, reduced pulmonary function, cognitive impairment and depression.

3. To extend, in a subset of patients, the range of analyses to novel vascular risk factors not measured in Phase I such as highly-sensitive C-reactive protein (hs-CRP), adiponectin, advanced glycation end-products (AGE), homocysteine, plasminogen activator inhibitor-1 (PAI-1) and N-terminal prohormone brain natriuretic peptide (NT-proBNP).

4. To assess bottom-up, patient-level, diabetes-attributable costs from a societal perspective.

Study population: All persons with known diabetes residing in the postcode-defined primary catchment area of Fremantle Hospital. The Princess Margaret Hospital arm is recruiting persons who attend any diabetes clinic at Princess Margaret Hospital.

Seven participants have been recruited from Princess Margaret Hospital since February 2010.

Funding Sources: NHMRC

Impact of hypoglycaemia on quality of life

TW Jones, S Johnson

The primary aim of this study is to determine the prevalence and impact of treatment-related hypoglycaemia and fear of hypoglycaemia on the quality of life of

young people with Type 1 diabetes and their families. Specifically, the study will examine the frequency of moderate and severe hypoglycaemia and its consequences on the quality of life of the patient and their family and its effect on glycaemic control.

Patients will be recruited during their routine 3-monthly clinic visit to Princess Margaret Hospital for Children, Perth. After consent is obtained, the child and /or parent will be asked to answer a number of validated questionnaires to determine the current impact of hypoglycaemia on their quality of life. These parameters include health-related quality of life, the fear of hypoglycaemia, level of hypoglycaemia unawareness, health utility and the utilisation of health resources as a consequence of hypoglycaemia.

Statistical analysis will be performed to examine the effects of the following factors on health-related quality of life: age and gender, rural or metropolitan dwelling, type of insulin therapy, glycaemic control expressed as HbA1c and duration of diabetes. The rate, fear and need to seek health resources for recent hypoglycaemic events will also be studied in relation to the individuals health related quality of life.

The study commenced in August 2009; 250 questionnaires have been completed and returned to date. It is likely to be completed by May 2010.

Funding: Medtronic

Disease Aetiology

TrialNet Natural History Study of the development of type 1 diabetes

TW Jones, EA Davis

The overall objective of this study is to perform baseline and repeat assessments over time of the metabolic and immunologic status of individuals at risk for Type 1 Diabetes (T1D) in order to:

- to characterise their risk for developing T1D
- to describe the pathogenic evolution of T1D
- to increase the understanding of the pathogenic factors involved in the development of T1D

This is an international study. The study population is blood relatives of individuals with T1D aged between 1-45 years. Those screened showing one or antibodies are invited to participate in phase 2 & 3, or they may be eligible for other studies. Those who are under 18 years who do not qualify for stage 2, are invited back for rescreening on an annual basis until they reach their 18th birthday. Those participants in phase 3 are seen at 6 monthly intervals for 5 years or until the end of the study. There are 369 participants involved in TrialNet in Western Australia

Funding Source: NIDDK; NAID; NICHD; NCR; JDRF; ADA

Molecular Signatures

G. Morahan, T.W Jones, J. Jooste

This study aims to identify genetic and molecular signatures to better understand the causes, triggers and progress of disease of T1D. This will be achieved by analysing the genetic and molecular signatures of the T1D disease process by analysing blood samples taken at diagnosis and again between three to eighteen months later. Sample size 100 newly diagnosed T1D participants aged 1-16 years, and without diabetes ketoacidosis at diagnosis. Participants recruited are those who will be attending the PMH clinics for follow-up.

So far 73 participants have had the first sample collected and stored and of this 37 have had second samples collected. Proteomics has been performed on a small sample of these complete sets, and results are being analysed.

Trials

Low Glucose Suspend Study

TW Jones, T Ly

Randomised controlled trial currently underway, involving participants must have type 1 diabetes with duration of at least 12 months. Currently on insulin pump therapy for at least 6 months. Subjects must have impaired awareness of hypoglycaemia, with HbA1c less than 8.5% and aged from 4 to 50 years. Adults will be recruited from adult tertiary hospitals (SCGH, FREQ, Rockingham, and RPH). The study will run for around 15 months. The

aim of the 'Low Glucose Suspend' study is to compare the use of CSII with real-time CGMS and low glucose suspend feature (the new VEO pump) versus CSII only (just continuing with their usual pump), in patients with type 1 diabetes who have impaired awareness of hypoglycaemia.

The primary objective is to determine the incidence of moderate and severe hypoglycaemia following 6 months of therapy with the CSII + Real time CGMS+ low glucose suspend feature versus CSII alone in patients with T1D with impaired awareness of hypoglycaemia. The hypothesis being that the incidence of moderate and severe hypoglycaemia will be reduced following 6 months of therapy with the CSII + Real time CGMS+ low glucose suspend feature, versus CSII alone. A subset of 16 adolescent and young adult participants will undergo a hyperinsulinaemic hypoglycaemic clamp procedure, pre- and post-intervention, to ascertain their counter-regulatory hormone and symptomatic responses during hypoglycaemia. Required sample size 100; 14 participants have been recruited to date.

Funding source: Medtronic

HypoMon Overnight Trials: Clinical Evaluation of the HypoMon hypoglycaemia detection device

TW Jones, V Skladnev, N Ghevondian, EA Davis

The HypoMon system is a non-invasive

hypoglycaemic detection device which has been previously successfully tested in three in-hospital clinical studies at Princess Margaret Hospital

The overall purpose of this study was to evaluate the ability of the HypoMon system to detect nocturnal hypoglycaemic episodes in Type I diabetic adolescents and young adults under usual insulin regimens. The specific aims of this study were to validate the HypoMon system design changes and enhancements made to the device subsequent to the Study III findings. The primary outcomes are the sensitivity and specificity of the device to detect hypoglycaemia during sleep. This study was conducted between September 2009 and March 2010. Analysis of 70 studies to date showed 78% sensitivity and 72% specificity.

The Clinical Trials is the next stage of the study, due to start in late July / early August 2010. The submission for this study has now been submitted to the Ethics Committee.

Funding Source: AiMedics Pty Ltd, Sydney, NSW.

Randomised Controlled Trial of the Bioenterics Intra-gastric Balloon (BIB) Versus Lifestyle Intervention Alone on Weight Loss and Reversal of Weight Related Diseases in Overweight Adolescents.

EA Davis; TW Jones; C Sherrington

The purpose of this randomized clinical trial is to determine whether the use

of the BIB aids weight loss in obese adolescents. Specifically, we hypothesise that:

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

Required sample size- 50. Adolescents aged 12-17y. Inclusion criteria is having a BMI z-score >2.5 and with comorbidities, or a having a BMI Z-score >3.0 and without co-morbidities. Those randomised to the intervention arm have the balloon inserted (stays in situ for 6months), and attend a 10 week life-style change program (CLASP), while those randomized to the control arm attend the CLASP program alone. The study duration is 4 years.

Two participants have now been randomized since Oct 2009 – one to the intervention arm.

Funding source: NHMRC, Pfizer, NHF

Adolescent Type I Diabetes Cardio-Renal Intervention Trial

EA Davis; TW Jones (WA)

The purpose of this randomized clinical trial is prevention of long-term diabetic complications. The primary objective to determine whether the taking of an ACE inhibitor and a cholesterol lowering

agent or a combination of both when compared to a placebo will reduce albumin excretion, reduce the incidence of microalbuminuria and reduce the incidence of microalbuminuria during the six month run out period following the completion of the intervention phase.

This is an international study involving United Kingdom, Australia and Canada. The sample population are adolescents aged >11 and <17 years. The study involves taking the study/placebo drugs for 3 years. They undergo baseline screening and regular screening including a 6 month run-out period. This involves 3 monthly visits with monitoring and renewing of their medication every 3 months. The study duration is 3-4 years. The target sample size for WA is 40; study commenced May 2009 (see table below).

Funding source: Diabetes UK, The British Heart Foundation and the Juvenile Diabetes Research Foundation

A randomised, Double-Blind, Placebo-Controlled Trial of Intra-nasal Insulin (40IU and 440IU) in Children and Young Adults at Risk of Type I Diabetes: Insulin Insulin Trial II

EA Davis, TW Jones

The primary objective of this study is to determine whether intra-nasal administration of insulin to children and young adults (aged 4-30years) at risk for type I diabetes (T1D) will reduce their rate of development of diabetes. At risk is defined by having a close relative with T1D, and screened as being double T1D biochemical antibody positive.

Those randomised have 3 monthly visits for the first year, during which they take the study medication. Participants will be followed until they develop diabetes or until 5 years after the last participant has been randomised (maximum period of follow-up expected to be 10 years).

The required sample size for Australia and New Zealand is 102 in the Clinical Trial Phase – 80 (from 112 screened positive for 2 antibodies -5540 screened) have now been recruited. In Western Australia 9 participants have now been randomised,

	Worldwide	Australia (Target 160)	UK	Canada
Consented to Study	92	40 (2 withdrawals)	26	26
Randomisation to study	76	32 (6 in WA)	18	26

with 2 participants yet to be randomised. One participant is yet to be staged.

Funding source: Diabetes Vaccine Development Centre

Complications screening

Brain structure and function in early-onset type 1 diabetes mellitus

TW Jones, EA Davis, T Ly

Children with an early-onset of type 1 diabetes show the most consistent evidence of cognitive dysfunction. A range of cognitive abilities are found to be affected, including but not limited to, declarative memory, spatial memory, attention and verbal IQ. However a variety of studies have also found little or no association between type 1 diabetes and cognitive ability. Results from our earlier study found intelligence quotient scores in the expected normal range and no significant group differences on the intellectual, memory or behavioural measures. However we found a high prevalence of CNS structural abnormalities (29%). Surprisingly, mesial temporal sclerosis (MTS) was detected in 16% of the total sample (see Table 2). The presence of MTS was not associated with a history of severe hypoglycaemia or diabetic ketoacidosis. Analysis of brain matter volumes suggested relatively less grey matter density in those with a history of severe hypoglycaemia.

The aim of the study is to examine the

long-term impact of severe hypoglycaemia on the cognitive and neurological function of children with early-onset type 1 diabetes – diagnosis before age 6 years. The participants had taken part in a previous study when the cohort had a mean age of 10 years. They have now been re-examined at a mean age of approximately 17 years. All testings have been completed, and the results are being analysed.

MA screening

TW Jones, EA Davis, A Sifarikas, G Price, C Choong, F Frazer

The aim of this international (UK, Canada and Australia) study is to identify subjects at high risk of developing diabetic nephropathy by measuring the mean albumin creatinine ratio (ACR) in 3 early morning urine samples of adolescents with T1D aged between 10.0 and 16.0 years, and greater than 1yr duration of diabetes without overt diabetes complications. Subjects within the upper tertile of the distribution of the mean ACR (adjusted for age, gender, age at onset and duration of diabetes) will be considered at high risk.

The high risk adolescents will then be invited to participate in a cardio-renalprotection intervention trial (AdDIT) and all adolescents from this study will be invited to enrol in a second follow-up study assessing cardiovascular and autonomic nervous function.

To date: 301 adolescents have been consented. 272 have provided 1st urines

and 175 have provided a second set.

Funding: NHMRC Enabling Grant

Does ambient blood glucose influence skin blood flow and microvascular function in adolescents with type 1 diabetes? : a validation study

TW Jones, EA Davis, D Green

The primary aim of this study is to determine whether ambient blood glucose levels affect microvascular function by manipulating blood glucose levels whilst simultaneously assessing microvascular function using the microdialysis and laser Doppler flowmetry techniques/iontophoresis. The secondary aim is to assess the reliability and relevance of the microdialysis techniques as a potential tool for assessing the early stages of microvascular abnormalities in this high risk population.

Hypothesis: Increased levels of blood glucose (hyperglycaemia) will reduce endothelium-dependent microvascular function in type 1 diabetic adolescents.

Potential significance: The effects of blood glucose on endothelium-dependent and nitric oxide (NO)-mediated microvascular function have not previously been directly assessed in vivo. Impairment in endothelial function may be the earliest detectable manifestation of future microvascular disease.

To date 10 clamp studies (n=12) have

been carried out to test the microdialysis technique – the preliminary results show a significance impact of hyperglycaemia (BGL 15mmol/L) on microvascular function.

Funding: NHF

T2D Macrovascular function

EA Davis; Louise Naylor; Danny Green

The aim of this study is to determine if adolescents with Type 2 Diabetes display impaired blood vessel function, compared to an age, sex and height matched control group. All adolescents attending the T2D clinic at PMH will be invited to participate in this study. Inclusion criteria are adolescents aged between 13 to 18y with a previous diagnosis of Type 2 Diabetes, who are attending any qualified paediatrician in WA. Age- and gender-matched controls will be recruited from the wider community. Blood vessel function will be determined using ultrasound to take images of the left & right carotid arteries, and to measure the width and speed of the blood flowing through the brachial arteries.

Eleven participants with Type 2 Diabetes have participated since December 2008. 10 age- and gender- matched healthy controls, and 10 age- and gender- matched obese controls have also been recruited.

Funding source: NHF

Exercise and T1D

Carbohydrate utilisation during exercise as a predictor of the risk of late-onset post-exercise hypoglycaemia in adolescents with type 1 diabetes: effect of different types of exercise

P Fournier, TW Jones, EA Davis

In order to prevent late onset post-exercise hypoglycaemia, patients with T1DM are currently advised to maintain stable blood glucose levels by increasing their carbohydrate intake and/or by lowering their insulin dose. Unfortunately current guidelines to advise those patients are clearly inadequate as a trial and error approach is advocated to determine the extent to which carbohydrate intake and insulin dose reduction should be altered in order to minimise the risk of late onset post-exercise hypoglycaemia. For these reasons, many individuals with T1DM are reluctant to adopt an active life style and are discouraged from participating in sports and games.

The hyperglycaemic effect of a prolonged bout of intense exercise raises the intriguing possibility that this type of exercise might be beneficial in preventing or delaying the onset of hypoglycaemia if no carbohydrate is readily available. Arguably, the problem here is that 10-15 minutes of exercise at high intensity is unlikely to be well tolerated by most individuals with T1DM due to the very intense nature and impractical duration of such an exercise bout. Recently we

examined whether a much shorter bout of exercise –10 s sprint- performed at maximal intensity could prevent glycaemia from falling in response to exercise or insulin. We found that a short 10-second sprint opposes effectively stabilises blood glucose levels for at least two hours, in part, by the marked rise in catecholamines and GH levels during early recovery. We have completed six paired studies and have enrolled the last two participants.

Funding: JDRF

Management of glycaemia during early and late recovery from exercise in type 1 diabetes: Measurement of hepatic glucose output and whole body glucose utilisation

P Fournier; TW Jones

Participation in regular physical exercise increases the risk of hypoglycaemia in those with T1D. Although exercise of moderate intensity in diabetic individuals in poor glycaemic control provokes a rise in blood glucose and ketone body levels, during exercise and also in the course of recovery. Furthermore, high intensity exercise causes an elevation of blood glucose levels in individuals with T1D, irrespective of their glycaemic control, and well after exercise has ceased.

The primary goal of this study was to determine the response of skeletal muscle glucose utilisation and liver glucose production to a 10-second all-out sprint, and to further explore further the

mechanisms responsible for the observed stabilisation period. Eight young adults with T1D and age & gender matched healthy controls were tested. The results show that for the first time that a short sprint can increase glycaemia in T1D individuals and suggest that this results from a transient decline in the rate of peripheral glucose utilisation. These patterns of glucose Ra and Rd responses to exercise are unique and markedly different from those associated with moderate or intense aerobic exercise. High catecholamines levels might contribute to the early fall in Rd post-exercise in diabetic individuals, but this interpretation must be reconciled with the finding that a similar pattern of change in the levels of those hormones is associated with little post-exercise changes in blood glucose levels, Ra and Rd in non-diabetic individuals.

Funding Source: JDRF

Staff and Students

Head of Group

Tim Jones MD, DCH, FRACP: Head, Department of Endocrinology & Diabetes, Princess Margaret Hospital for Children; Clinical Assoc Prof, Centre for Child Health Research

The University of Western Australia; Adjunct Professor, Institute for Health & Rehabilitation Research,

The University of Notre Dame

Research Staff

Elizabeth Davis MBBS, FRACP

Nirubasini Paramalingam BSc(Hons), H Dip(Children's Nursing),DE

Heather Roby BSc

Rachelle Kalic BPsych

Ray Davey BSc(Hons),

Barbara Sheil, PhD

Joel Ives B Psych student

Aveni Haynes MBBS,

Angela Reeves BSc(Hons)

Max Bulsara MSc, PhD

Jane Ventouras BSc (Hons)

Affiliated Research Staff (PMH)

Aris Siafarikas MD FRACP

Jacqueline Curran MBBS

Trang Ly MBBS, DCH

Stephanie Johnson MBBS

SM O'Connell BMedSc; MBBS; MRCPI (Child Health); MD; Cert. Higher Specialist Training in General Paediatrics

Julie Dart RN

Julie Kendall B Nursing, PG Dip Comm Health

Postgraduate Students

Elizabeth Davis PhD candidate

Ray Davey PhD candidate

Aveni Haynes PhD candidate

Trang Ly PhD candidate

Jacqueline Curran PhD candidate

Nirubasini Paramalingam PhD candidate

Research Support

Mary Flynn BA, PG Dip in Counselling

Theses passed

Sarah McMahon FRACP, PhD

Max Bulsara MSc, PhD

Awards (2009)

T Ly: Telethon Research Fellowship, 2010;
Kelva Campbell Fellowship, Diabetes
Research Fund, 2009; APEC Research
Grant, 2009

External Committees

International

A Siafarikas: German Centre for Growth
and Development of Children and
Adolescents, Berlin, Germany

National

TW Jones: Member Medical Advisory Panel,
Diabetes Research Foundation of Western
Australia 2002- ; Member Scientific Review

Committee Diabetes Australia Research
Trust 2004- ; Organising Committee –
Best Practice in Paediatrics Committee,
2010

EA Davis: APEG Diabetes Database
Committee, APEG; Education
subcommittee, APEG; National committee
for development of consensus guidelines
for Polycystic Ovary Syndrome; Tertiary
Obesity Clinical Networks – Executive
committee; member of Australian Child
and Adolescent Obesity Research Network
committee; Advisory member of Birth
Defects Registry; Board of Diabetes
Research Foundation; Board of Child
Health Research Foundation

Local

TW Jones: Princess Margaret Hospital
Prioritisation Committee 2007- ; Executive
Member

Endocrine Network, Department of Health
2006- .

Invited Presentations

Tim Jones:

1. Insulin Pump Therapy. Australian
Paediatric Society, 3rd Annual Insulin Pump
Workshop, Newcastle, NSW. March 2009;
2. Intensive Insulin Therapy. Lawson Wilkins
Paediatric Endocrine Society/European
Society for Pediatric Endocrinology, New
York, September 2009;
3. Growth and Puberty in Children.

Australian Pituitary Foundation WA, Perth,
September 2009;

4. Paediatric Endocrine Disorders and
Fertility. Fertility Nurses Association of
Australia, Perth, WA. October 2009;

5. Closing the Loop – Australian
perspectives on Artificial Pancreas Project.
ADS Medtronic Symposium. Adelaide,
2009.

Elizabeth Davis:

1. T2D in WA – Annual meeting of WA
Diabetes Educator Association. Perth, May
2009

2. Management of Diabetes Mellitus
in Isolated Aboriginal Populations.
Lawson Wilkins Paediatric Endocrine
Society/European Society for Pediatric
Endocrinology, New York, September 2009

Aris Siafarikas:

1. Metabolic Emergencies – Addisonian
Crisis and Diabetic Ketoacidosis. National
Conference for General Practice, Perth,
WA, Australia

Drug Discovery Technology Unit

Overview

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

- i) A discovery contract was signed between Phylogica and Europe's largest pharmaceutical company Roche
- ii) Collaborative agreement signed with Cambridge based Isogenica aimed at rapid optimization of our Phylomer peptides.
- iii) Our libraries and screening processes have been significantly expanded and enhanced
- iv) We have obtained potent antimicrobial Phylomer peptides with activity against resistant clinical isolates of important bacterial agent of hospital based infections, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
- v) Collaboration with the Cambridge University/MRC Hutchison Institute shows very high hit-rates from Phylomer libraries in phenotypic screens to discover new targets.

Roche

A contract was recently signed with Roche, one of the world's largest pharmaceutical companies. Roche is now the largest in the 'biologics' (large molecule drugs) space

We are not aware of such a contract discovery deal ever having been done by an Australian biotechnology company with

Roche, so we are delighted to have been chosen as their partner. This deal provides Phylogica with a revenue stream and access to downstream milestone payments and royalties as Roche take candidates discovered from our libraries through the preclinical and clinical development process. The Drug Discovery Technology Unit is now working with Roche's biologics R&D team using Phylomer peptides as targeting agents, to enhance our opportunities for discovery of a number of different drugs by transporting them into cells.

Improving Phylomer Libraries and Screening Process

Phylogica's current libraries are the most structurally diverse biologics discovery libraries available with billions of compounds from thousands of shape families. This vast diversity of shapes means more hits can be obtained against a wider variety of targets.

Over the past few months, as the company has been gearing up for its contracted commercial projects, there has been a strong focus on the expansion of all libraries (8 new libraries were constructed in 2009) and the optimising of the screening processes. Encouragingly, efforts to improve the drug-like properties of hits in our advanced CD40L programme have met with significant success. For example, simply by using the new libraries and optimising the screening conditions we have obtained hits which are 50-times

as potent as our current lead candidates. The Drug Discovery Unit has identified primary hits from our libraries with very high affinities (picomolar Kd) for their targets.

Blocking The Inflammation Target CD40 Ligand (CD40L)

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

Collaboration With Cambridge University / Mrc Hutchison Intitute.

The Drug Discovery Technology Unit has been collaborating with the distinguished Professor of Oncology Ashok Venkitaram of the Hutchison MRC Unit at the University of Cambridge in the UK. The objective has been to test if Phylomer libraries might assist in identifying new cancer targets for the discovery of new drugs. The Hutchison group has shown the Phylomers can bind to defined targets linked to cancer cells, and that the hit-rate in a phenotypic mammalian screen

of a Phylomer library is superior to that from traditional approaches used by pharmaceutical companies. Having achieved this aim, the next relevant step was to use the target binding as a tag to identify the key biological step in a pathway for which new drugs might be built. The success of the target identification using the Phylomers in this collaboration highlights the usefulness of this approach for target discovery.

Staff and Students

Head of Unit:

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

A leading graduate from The University of Western Australia, Paul Watt completed his doctorate in Molecular Biology at Oxford University before taking up postdoctoral appointments in yeast genetics at Harvard and Oxford. Working in genomic instability, Dr Watt cloned two novel genes *SGS1* and *PAT1* and characterized the function of these proteins. *SGS1* is the yeast homologue of the human Bloom's and Werner's syndrome genes. As an Honorary Research fellow at the Telethon

Institute for Child Health Research, he was appointed Adjunct Professor at the school of Paediatrics and Child Health of the University for Western Australia. Professor Watt has published more than 40 peer-reviewed scientific papers (including several which have been cited hundreds of times). As an inventor on 19 patent applications (including several granted in US and Europe), he founded InfaMed Ltd., which is commercialising a drug delivery device, which he developed for asthmatic children. This device, which has received US regulatory clearance from the FDA and is CE marked, is currently marketed in Australia and overseas by Avita Medical (www.avitamaterial.com). Professor Watt is currently CEO of Phylogica (www.phylogica.com), a public drug discovery company, which he founded to commercialise a novel class of peptide being developed by his laboratory known as Phylomers.

Richard Hopkins BSc (Hons), PhD
Chief Operating Officer and VP Research for Phylogica

Richard Hopkins completed his PhD in Molecular Parasitology before taking up a postdoctoral appointment in yeast genetics at the Institute for Child Health Research in Western Australia. His work focussed on development of a novel class of peptides, referred to as Phylomers, and the methods to integrate them into various high throughput screening platforms such as yeast two hybrid and phage display. More recently, his work has focussed

on engineering peptide leads for drug development. Dr Hopkins has published over 20 peer reviewed papers and is a co-inventor on approximately 10 patent applications, several of which have been issued in the US and Europe. Dr Hopkins is a founding member of Phylogica, a publicly listed company aiming to commercialise the development of therapeutic Phylomer peptides. Dr Hopkins is currently the Chief Operating Officer and VP Research at Phylogica.

Research Staff:

Katrin Hoffmann BSc (Hons), PhD

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Colin Thompson BSc (Hons), PhD

Suzy Juraja BSc (Hons), MSc, PhD

Shane Stone BSc (Hons), PhD

Yanming Zou BSc (Hons), MSc, PhD

Heique Bogdawa BSc, MSc, PhD

Karen Kroeger BSc (Hons), PhD

Paula Cunningham BSc (Hons), PhD

Tatjana Heinrich BSc (Hons), PhD

Mark Anastasas BSc (Hons)

Rebecca Hellsten BSc (Hons)

Marie Scobie BSc (Hons)

Lan Doan BSc (Hons)

Clinton Hall BSc (Hons)

Scott Winslow BSc (Hons)

Susan Aulfrey BSc (Hons), PhD

Support Staff:

Leanne Neville

Farzana Khan BSc

External Committees

International:

- Cambridge Healthtech Institute Conference Faculty for PepTalk, San Diego
- Conference faculty IBC and Protein Engineering, San Francisco

Local:

- Committee for AusBiotech, Western Australia
- UWA Pathfinder committee for commercialisation grants
- Non executive director of ASX listed AVITA Medical Limited

Invited Presentations

Jan 13 -18 CHI PepTalk, San Diego

May 22 – 24 International Congress of Antibodies, Beijing

June 25 Biopartnering China, Tianjin

June 26 – 28 BioEco 2009 China Conference, Tianjin

Sept 21-23 IBC Beyond Antibodies San Diego

Sept 30- Oct 2 Roche Biologics, Boulder

Oct 11- 13 Biopartnering Europe, London

Oct 14-15 GTC Bio 5th Modern Drug Discovery Summit, San Diego

Oct 29-30 Oxford Global 2nd Annual Proteins Congress, Berlin

Nov 2-4 BioEurope, Vienna

Genetics and Health Laboratory

Overview

Research in the Genetics and Health Laboratory (GHL) at TICHHR is mostly about understanding genetic risk in disease and how this influences, or is influenced by, environmental risk factors. We also do research that is primarily designed to lead us to novel vaccine candidates for parasitic infection. Senior members of the GHL, Jenefer Blackwell, Sarra Jamieson and Christopher Peacock, have had a long term interest in infectious disease, particularly bacterial and parasitic diseases. At TICHHR the group has established family studies of ear infection in non-Indigenous children in Western Australia (WA) and of ear health and metabolic diseases including type 2 diabetes (T2D) in a WA Aboriginal population. We are also using genetics, gene expression and studies of metabolism to understand why T2D is a major risk factor for bacterial sepsis in Thailand. Sarra Jamieson, who leads the ear health studies, also has a major interest in epigenetic regulation of genes that influence susceptibility to complex disease, and is applying this approach to understand the increased incidence of hypospadias in Australian boys. Jenefer Blackwell, Head of the GHL, retains a position as Honorary Senior Scientist and Affiliated Principal Investigator at the Cambridge Institute for Medical Research (CIMR), University of Cambridge, UK, allowing her to maintain a small laboratory in Cambridge which focuses on host genetics and parasitic disease research. Christopher Peacock focuses his research on understanding more about genetics

of bacterial and protozoan pathogens. During 2009 he was awarded an ARC Future Fellowship which has allowed him to establish an independent laboratory in the School of Biomedical, Biomolecular & Chemical Sciences at UWA. He retains an honorary position at TICHHR and maintains close ties with the GHL. His collaborative projects with the GHL are included in this report, as are the projects from the CIMR laboratory.

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

Genetics of Complex Disease

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

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

Understanding health and disease in Aboriginal communities could play an important role in reducing the disparity between Aboriginal and non-Aboriginal populations in Australia. The aim of this project is to use genetics as a tool to understand more about the pathogenesis of disease in Aboriginal Australians. During 2008 a partnership was established between the Ngangganawili Aboriginal

Health Service (NAHS) and TICHHR, underpinned by the signing of memoranda of understanding (MoU) between NAHS and TICHHR, and between NAHS, Karalundi Aboriginal Educational Community Inc. (KAEC; which is serviced clinically by NAHS) and TICHHR. These MoUs incorporate the principles for research in Aboriginal communities as outlined within the framework of the NHMRC and other national guidelines. The family study of ear health and metabolic diseases was approved by the WA Aboriginal Health and Information Ethics Committee (WAAHIEC) in 2009.

This study is examining genetic susceptibility to otitis media in children, and genetic risk factors for metabolic diseases such as type 2 diabetes (T2D), heart disease, renal failure, and obesity in adults. Collection of saliva for DNA commenced in November 2009, and by January 2010 we had over 300 fully consented DNA samples. We are on target to achieve 750-1000 samples needed for a full SNP-chip genome-wide association study (GWAS) of these diseases by the end of 2010. Clinical and quantitative trait data have been mapped onto around 20 large inter-related pedigrees, and heritability for quantitative traits has been estimated; e.g. body mass index is ~55% heritable, which is in line with published international studies. Pilot SNP-chip analysis of family founders is in progress, as are association studies and re-sequencing of major genes known to be associated with obesity/T2D in Caucasian, Asian and African populations.

Candidate gene studies that build on our observations in the Perth-based study of Caucasian children (cf. below) with otitis media are in progress. The results of these studies should be broadly applicable to other WA Aboriginal communities, and could inform treatment and translational research strategies across Aboriginal and Torres Strait Islander communities.

Funders of the project: The NHMRC

Candidate gene and genome-wide association studies of otitis media

*Sarra Jamieson (Project Leader), Jenefer Blackwell, David Burgner, Harvey Coates, *Heather Cordell, Richard Francis, Joyce Oommen, Peter Richmond, Marie Rye, Elizabeth Scaman, Shyan Vijayasekaran, Selma Wiertsema, (* International Partner)*

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. In Australia in 2008, OM resulted in a net cost of lost wellbeing (i.e. cost of morbidity, lost parental earnings etc) of \$1.05-\$2.6 billion. 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 recurrent acute otitis media (rAOM) is highly heritable.

To identify the genes that contribute to rAOM, we established the Family Study of Ear Infections in Western Australian (WA) Children (<http://www.ichr.uwa.edu.au/om>). During 2009 we reached a sample size of 600 in our quest for 1000 families/trios. DNA has been prepared from more than 1800 saliva samples collected from children with rAOM 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. During 2009, a web-based questionnaire database was developed by our bioinformatician, and data entered for qualitative and quantitative information on disease history and environmental risk factors or covariates. Mouse-to-man hypothesis-driven candidate gene analysis was undertaken and has demonstrated the importance of the TGF pathway in susceptibility to rAOM. These findings have been replicated by directed analysis of available genome-wide Illumina 660 Quad chip data for 428 children with recorded ear health problems compared to 1104 phenotype-clean controls from within the WA Pregnancy (Raine) Cohort Study. Funding proposals are under consideration to carry out a full GWAS in WA comparing 1245 rAOM cases with available control data from the Raine Cohort and the Wellcome Trust Case Control Consortium (WTCCC). Deep replication analysis will be undertaken in >2400 rAOM cases from the OTIGEN consortium comprising laboratories from USA, UK and mainland

Europe. This will provide a powerful resource to identify the genetic risk factors for rAOM, to analyse gene x environment interactions, and to gain unique and novel insights into the pathogenesis of rAOM that can inform future intervention strategies.

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

Genome-wide association study of visceral leishmaniasis

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

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

in susceptibility could provide important leads for improved therapies.

During 2008-2009 we have been undertaking a GWAS of visceral leishmaniasis and the quantitative DTH trait using 4880 DNAs (India, Brazil, Sudan) genotyped on the Illumina 660 Quad chip as part of phase 2 of the Wellcome Trust Case Control Consortium (WTCCC2). Primary GWAS was complete 2009, and deep replication is in progress. Results are under embargo, but the major result is exciting and is likely to impact on how we approach vaccine development. Ongoing projects in the lab are designed to capitalize on all of the output of the GWAS to identify functional pathways in pathogenesis, knowledge of which can impact more broadly on the development of novel therapies and interventions.

Funders of the project. The Wellcome Trust and the NIH

Genetics and epigenetics of hypospadias

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

Hypospadias is a congenital malformation of the male genitalia whereby the urethral opening develops on the ventral (underside) surface of the penis, or on the scrotum or perineum as a result of

abnormal urethral closure between 8 and 14 weeks gestation. Most hypospadias cases require major surgical repair at 1 year to ensure urinary function and fertility in the long term. Research carried out at TICHR by Natasha Nassar indicates that in Western Australia hypospadias is the second most common birth defect among boys affecting, 1 in every 170 male infants, with rates doubling over the last 25 years. The aetiology of hypospadias is largely unknown, but an underlying disturbance in endogenous hormone production has been identified as a key causal mechanism. Preconceptional (maternal or paternal) or in utero (maternal) exposure to endocrine disrupting chemicals (EDCs), environmental agents with oestrogenic or anti-androgenic effects, has been proposed as a potential risk factor. To date, the biological mechanisms of action of EDCs remain to be elucidated. In 2008, a collaboration was established with Natasha Nassar in the Division of Population Sciences to address how genetic and/or epigenetic variation in response to such EDC exposure may contribute to the aetiology of hypospadias. This forms the basis to expanding research on congenital diseases and builds on the strong history of analysis of birth defects at TICHR. Funding proposals are under consideration to carry out genome-wide methylation analyses in relevant tissue samples.

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

Genetics at the interface between

type 2 diabetes and infection in Thailand

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

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

help to define immunological, biochemical, metabolic, and molecular pathways that are important in determining heritable and environmental risk, pathogenesis, and the interplay between T2D and sepsis.

Funders of the project. Commission for Higher Education, Thailand

Parasite Genomics and Vaccine Studies

Collaborative development of a vaccine against cutaneous and visceral leishmaniasis

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

Leishmania are protozoan parasites that cause severe and debilitating cutaneous, as well as fatal visceral, disease in sub-tropical/tropical regions of Old and New Worlds. There are no vaccines in routine use. Despite the need for vaccines, there are challenges facing Leishmania vaccine development: (1) to find a vaccine that will cross-protect against the different forms of disease [i.e., visceral, cutaneous, or mucosal leishmaniasis]; (2) to induce long-lasting immunity, and (3) to identify key immune responses in vaccine-induced protective immunity. This project represents a collaborative effort between three laboratories working on the unified theme of vaccine development against leishmaniasis. In Cambridge, the Blackwell laboratory used DNA vaccination in mice

to screen 100 unique Leishmania genes as vaccine candidates against high dose virulent *L. major* infection. Fourteen novel and reproducibly protective antigens were identified. Mary Wilson's lab at the University of Iowa discovered six novel antigens through cDNA library screening with immune serum and T cells. At Yale University, Diane McMahon-Pratt's lab had 4 well-characterized antigens which protected against *L. amazonensis* and/or *L. infantum* infection. During 2009 worked continued to determine which of a selection of 20 of these novel antigens are cross-protective against cutaneous and visceral Old World and New World Leishmania spp. in mice, and to determine whether alphaGalCer used as adjuvant with DNA enhances protective immune responses and vaccine efficacy. Peptide pools for 10 of these vaccine candidates were also used as antigens in antibody and T cell assays in blood samples taken from dogs or humans naturally infected with *L. infantum chagasi* in Brazil. By looking at the antibody and cytokine profiles associated with active or cured disease, and in dogs or humans exposed but resistant to infection, we are beginning to build a picture as to which antigens elicit potentially protective immune responses in dogs and humans. This has now been extended to study all 20 antigens, and to study humans naturally infected with *L. donovani* in India. Ultimately, the combination of murine, canine and human data will be used to determine the best cocktail of these antigens to be taken forward into canine and/or human trials to

reduce the incidence of human disease. Funders of the project. NIH.

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

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

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

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

Funders of the project: Pfizer Inc.

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

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

Leishmaniasis is a major global disease that affects millions and kills many thousands of people. There are no vaccines, prophylaxis and the few drugs that are available are toxic and difficult to deliver. This project is using the non-human pathogenic strain of leishmania recently discovered in Australian marsupials as a model to identify and characterize genes that determine pathogenicity in humans. During 2009 work commenced on sequencing the genome of the kangaroo leishmania, data from which is being compared to the publicly available genomic sequences for species representing the full spectrum of human disease. Genes identified in pathogenic but not non-pathogenic leishmania will be cloned and transfected into the kangaroo leishmania and the

transfected parasites studied for their effects in vitro in human cells and in vivo in mice. Kangaroo leishmania overexpressing known candidate vaccine antigens will also be used to develop a potential attenuated vaccine that will be tested in the mouse model of infection.

Funders of the project. NHMRC and ARC Future Fellowship

Staff and Students

Head of Laboratory

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

GHL:

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

Prasong Khaenam BMedTech(Hons), MSc,
PhD (Visiting Scientist)

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

Elizabeth Scaman BA(Hons)

Genevieve Syn BSc(Hons)

UWA Lab:

Christopher Peacock BSc, FIMLS, PhD

Ace Yu Leng Choo BSc(Hons), MSc

Wei Lu BSc(Hons), PhD

CIMR Lab:

Michaela Fakiola BSc(Hons), MSc, PhD

E. Nancy Miller BA(Hons), PhD

Postgraduate Students

Audrey Appudurai BSc, Honours Candidate
(UWA, Peacock Lab)

Surachat Buddhisa BSc(Hons), MSc, PhD
Candidate (Thailand)

Richard Francis BSc(Hons), MSc, PhD
Candidate (UWA)

Rohini Gupta BSc(Hons), Masters
Candidate (UWA, Peacock Lab)

Tereena Lucas BSc Honours Candidate

Sanjana Mehrotra BSc(Hons) PhD
Candidate (India)

Anshuman Mishra BSc(Hons) PhD
Candidate (India, CIMR Lab)

Marie Rye BSc(Hons) PhD Candidate
(UWA)

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

Awards

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

Jenefer Blackwell, ScD, University of
Cambridge, UK

Christopher Peacock, ARC Future
Fellowship

External Committees

International

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

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

National

Jenefer Blackwell, Chairman NHMRC
Fellowships Panel, 2009

Local

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

Sarra Jamieson, WA DNA Bank
Management Committee, 2009+

Sarra Jamieson, Treasurer, Perth
Epidemiology Group, 2008+

Invited Presentations

Jenefer Blackwell, World Leish IV, Invited Participant (3 posters with postdoctoral staff), 3-7 February 2009, Lucknow, India.

Jenefer Blackwell, Inaugural meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Co-convenor and Speaker, 7-8 February 2009, Varanasi, India.

Jenefer Blackwell, African Society for Human Genetics, Invited Speaker, 12-15 March 2009, Yaounde, Cameroon.

Jenefer Blackwell, Frontiers Meeting Genetic Diversity in Health and Disease in African Populations, The Wellcome Trust and The National Institutes of Health, Invited Participant, 15 - 16 March 2009, Yaounde, Cameroon.

Christopher Peacock, Faculty of Associated Medical Sciences, Associated Medical Sciences 30th Anniversary Conference, Invited Speaker, 17-19 March 2009, Khon Kaen, Thailand

Sarra Jamieson, Faculty of Associated Medical Sciences, Associated Medical Sciences 30th Anniversary Conference, Invited Speaker, 17-19 March 2009, Khon Kaen, Thailand

Jenefer Blackwell, Europe-Africa Frontier Research Conference Series "Infectious Diseases: From Basic to Translational Research", Invited speaker, 4-9 April, The Cape Winelands, South Africa.

Jenefer Blackwell, The Australian Society for Microbiology Golden Jubilee Year AGM,

Invited Plenary Speaker, 6-10 July 2009, Perth Convention and Exhibition Centre, Western Australia.

Christopher Peacock, The Australian Society for Microbiology Golden Jubilee Year AGM, Invited Plenary Speaker, 6-10 July 2009, Perth Convention and Exhibition Centre, Western Australia.

Jenefer Blackwell, Perth Epidemiology Group, Invited Speaker, 11 November 2009, Perth, Western Australia.

Inflammation Laboratory

Overview

In the last few years we have studied the ability of UV light, similar to sunlight, administered to the shaved dorsal skin of mice, to suppress models of allergic airways disease. This suggested that UV-induced changes in the skin could signal downstream systemic responses to allergens in respiratory tissues. In 2009, we further detailed the cellular mechanisms by which UVB light is immunomodulatory at the time of disease expression. The hypothesis had been that UV-induced an IL-10-producing T regulatory cell. However in extensive searches of cells in the trachea and airway draining lymph nodes, we were not able to detect regulatory cells of any type. Instead the reduced responses to allergen challenge were due to fewer allergen-specific effector T cells. In parallel studies we have investigated the effects of UV-induced vitamin D3 in control of immune cell activity in vitro, as well as control of asthma models in mice. Humans obtain 90% of their vitamin D3 from UV irradiation of skin so it has been proposed by us, and others, that UV-induced Vitamin D3 may contribute to the immunomodulatory effects of UV. We examined the effect of vitamin D3 in excess (painted onto the skin of mice with normal levels of vitamin D3) and in deficiency (mice were fed diets restricted in vitamin D3). These studies suggest that vitamin D3 is immunosuppressive in hypersensitivity and asthma models. In other studies of the consequences of UV irradiation of skin, we have investigated

changes in the bone marrow of UV-irradiated mice. When bone marrow cells are cultured with cytokines to induce dendritic cell development, the cells from UV-irradiated mice have poor priming ability for immune responses. In 2009, our studies suggested that UV-induced prostanooids in mice signal changes to bone marrow cells that imprint changes on dendritic cell precursors. Studies are continuing to better understand the biological mechanisms involved. In 2009, our studies of the mechanism of action of interleukin-4 as an anti-inflammatory cytokine for human monocytes and macrophages have continued. We hypothesised that Suppressor of Cytokine Signalling-1 (SOCS-1) may be responsible for the immunoregulatory properties of IL-4 as it was a new molecule induced in monocytes within 60 minutes of exposure to IL-4. However, studies did not confirm our hypotheses. Gene arrays are now giving us new candidate molecules that may be involved in the mechanism by which IL-4 suppresses inflammatory mediator production.

Immunomodulatory effects of UVB radiation on inflammatory airways disease in mice

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

We have previously shown that UV irradiation of skin causes a systemic suppression of immune responses. More specifically, UV irradiation of skin

suppressed the expression of two asthma models in mice. We have analysed the effect of a single exposure to UV for a time equivalent to about 20 minutes in noon in summer in Perth. In the first model, the allergen was the cysteine protease, papain. In the second model, mice were sensitised to ovalbumin mixed with the adjuvant, alum. Airways hyperreactivity was significantly reduced by exposure to UV, as well as the levels of inflammatory cytokines in lavage fluid and antigen-specific responses by cells from the lung-draining lymph nodes. Our hypothesis was that UV-induced CD4+CD25+ cells were responsible for reduced allergic airways disease. We extensively sought this cell in the trachea and lymph nodes of UV-irradiated, ovalbumin-sensitised mice at the time of allergen challenge (at least 3 weeks after UV-irradiation). Instead of a UV-induced CD4+CD25+ regulatory cell, we consistently detected more ovalbumin-sensitised effector CD4+CD25+ cells in the airway tissues. The possibility of other UV-induced regulatory cells was examined but again, no regulatory cells were identified. We now have preliminary data that UV induces a short lived CD4+CD25+ regulatory cell that can be detected 7 days but not 21 days post-UV-irradiation. Studies are ongoing to gain a better understanding of the mechanism by which UVB radiation can modify some of the important pathological components of asthma, and the optimal time of UV delivery. These studies will contribute to a basic understanding of the immunological events in asthma development and how

they can be modified by UV irradiation of skin.

Funded by NHMRC

Vitamin D in excess – Effects of topical vitamin D3

S Gorman, M Judge, PH Hart

Skin keratinocytes have an autonomous vitamin D pathway and can produce substantial amounts of 1,25(OH)₂vitamin D3, the hormonally active form of vitamin D3, when exposed to UVB light. We propose that levels of 1,25(OH)₂vitamin 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)₂vitamin D3 applied directly to skin. The concentration of 1,25(OH)₂vitamin D3 was based on studies in UV-irradiated human skin. Application on skin of 1,25(OH)₂vitamin D3 enhanced the regulatory capacity of non-antigen-specific CD4+CD25+ cells in the draining lymph nodes. When purified from these nodes, and transferred into allergen-prensensitised mice, the immune response in the airways of recipient mice to aerosolised allergens was reduced. The immune properties of CD11c+ dendritic cells from draining lymph nodes of mice topically painted with 1,25(OH)₂vitamin D3 have also been studied. Upon adoptive transfer, they were less efficient at priming immune responses. We propose that these CD11c+ cells are responsible

for reduced regulatory activity of CD4+CD25+ cells. These results suggest that 1,25(OH)₂vitamin D₃ formed upon UV irradiation of skin may contribute to the immunomodulatory effects of UV irradiation of skin, as well as the enhanced health of our immune system.

Funded by NHMRC and Asthma Foundation of WA

Mechanisms of immunomodulation by vitamin D3

S Gorman, M Judge, PH Hart

We have investigated the ability of 1,25(OH)₂vitamin D₃ to directly regulate CD4+CD25+ T regulatory cells from lymph nodes of mice. Initially we analysed mRNA levels for Th1-Th2-Th3 cytokines expressed by CD4+CD25+ and CD4+CD25- cells from lymph nodes draining sites of topical 1,25(OH)₂vitamin D₃ administration. mRNA levels for IL-2 and TLR4 were consistently up-regulated in CD4+CD25+ cells. Subsequent studies showed that similar increased IL-2 and TLR4 mRNA levels in CD4+CD25+ cells exposed to both 1,25(OH)₂vitamin D₃ with IL-2 in vitro. Functional studies have confirmed that IL-2 enables 1,25(OH)₂vitamin D₃ to directly stimulate CD4+CD25+ T regulatory cells. These studies suggest that with IL-2, 1,25(OH)₂vitamin D₃ can have direct effects of CD4+CD25+ cells, as well as indirect effects via actions on CD11c+ dendritic cells.

Funded by NHMRC and Asthma Foundation of WA

Vitamin D in deficiency – Effect of diets deficient in vitamin D3

D Tan, S Gorman, PH Hart

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

Funded by Asthma Foundation of WA

Effect of UVB on bone marrow-derived dendritic cells

R Ng, J Bisley, S Gorman, PH Hart.

In response to erythral amounts of UV, there is inflammation of the skin. Signals

are then sent from the skin to the bone marrow, via the lymph nodes, such that new immune cells are produced that can be involved in the inflammatory response. The phenotype and function of cells isolated from the bone marrow of animals administered a single acute oedematous dose of UV have been studied. Dendritic cells derived from the bone marrow of UV-irradiated mice were significantly less efficient at presenting antigen to T cells in vivo. When the mice were implanted with slow release indomethacin pellets prior to UV-irradiation, the regulatory effects of UV on bone marrow CD11c+ cells were removed. We are studying the mechanisms by which UV-induced prostanooids regulate the development of CD11c+ cells. Gene targeted arrays have identified molecules that are increased in CD11c+ cells from bone marrow of UV-irradiated mice, but which are no longer present in bone marrow cells from mice treated with indomethacin before UV irradiation. We are further analysing the identity and function of these molecules.

Funded by NHMRC

Mechanisms of regulation by IL-4 for reduced inflammatory mediator production by human monocytes

E Woodward, PH Hart.

We have been studying the mechanisms by which interleukin-4 (IL-4) can suppress inflammatory cytokine production by activated human monocytes and macrophages. 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. mRNA and protein for SOCS-1 were measured in IL-4-treated monocytes and macrophages. Correlations were investigated between regulation of TNF production and SOCS-1 expression. No data supported the involvement of SOCS-1 in the regulatory properties of IL-4. By extensive Western blotting for phosphorylated proteins and functional inhibitor studies, there was no evidence that IL-4 negatively regulated MAP kinase activity. Using gene arrays, we continue to search for molecules that may be involved in the anti-inflammatory properties of IL-4.

Funded by Murdoch University Students stipend

Staff and Students

Research Staff

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

Shelley Gorman BSc (Hons) PhD

Melinda Judge BSc (Hons)

Misty Lambert BSc (Hons)

Jacqueline McGlade BSc (Hons), PhD, until May 09

Jacqueline Bisley BSc, BSc (Hons)

Postgraduate Students

Eleanor Woodward BSc (Hons), PhD Candidate

Royce Ng BSc (Hons), PhD Candidate

Daryl Tan BSc, Hons Candidate

Awards

Prue Hart

Adjunct Professor, University of WA,
NHMRC Principal Research Fellowship

Shelley Gorman

Adjunct Senior Lecturer, Richard Walter
Gibbon Medical Research Fellowship,
University of Western Australia, Faculty of
Medicine and Dentistry.

Daryl Tan

Honours 1st class, Murdoch University, The
effects of vitamin D deficiency in utero and
early childhood on asthma

Presentations

PH Hart

Invited symposium speaker, Lung Institute
of WA 10th birthday 2-day symposium,
March 2009

Presenter, 15th International Congress for
Photobiology, Dusseldorf, Germany, June

2009.

Invited symposium speaker, Mutagenesis &
Experimental Pathology Annual Meeting,
Sydney, November 2009

S Gorman

Invited talk: Department of Microbiology
and Immunology Seminar Series, University
of Western Australia, Perth, May 2009.

Invited talk: Department of Pathology
Lecture Series, Royal Perth Hospital, Perth,
June 2009.

Invited talk: Lung Research Group Seminar
Program, Department of Respiratory
Medicine, Sir Charles Gairdner Hospital,
Perth, August 2009.

Invited talk: Laboratory for Experimental
Medicine and Endocrinology, Katholieke
Universiteit Leuven, Leuven, Belgium,
October 2009.

Poster: The 14th Vitamin D Workshop,
Brugge, Belgium, October 2009.

Poster: The 39th Australasian Society
for Immunology Annual Scientific
Meeting Vitamin D Workshop, Gold Coast,
Australia, December 2009.

External Committees.

PH Hart

Chair, NHMRC Career Development
Award Sub-Committee.

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

Member, Cure Cancer Australia Scientific
Committee

S Gorman

Convenor, Organising Committee, ASMR
Medical Research Week, June 2008.

Leukaemia and Cancer Research

Overview

Cancers in children comprise many different diseases. More than half of them affect cells of the immune system and the central nervous system, while only a minority 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 tumour 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

Interactions between acute lymphoblastic leukaemia and bone marrow stromal cells influence response to therapy

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

The cure rate for paediatric patients with B-cell precursor acute lymphoblastic leukaemia (BCP- ALL) is steadily improving, however relapses do occur despite initial response to therapy. To identify links between drug resistance and gene deregulation we used oligonucleotide microarray technology and determined in 184 BCP-ALL specimens the genes differentially expressed compared to normal CD34+ cells. We identified 20 signature genes including CTGF, BMP-2, CXCR4 and IL7R that are documented to regulate interactions in the bone marrow. We recorded remarkably similar levels of expression in three independent patient cohorts, and found distinct patterns in cytogenetically defined subgroups of BCP-ALL. The canonical pathways that

were affected are involved in inter- and intra-cellular communication, regulating signalling within the microenvironment. We tested experimentally whether interaction with stromal cells conferred protection to four drugs used in current ALL therapy, and demonstrated that bone marrow stromal cells significantly influenced resistance to vincristine and cytosine arabinoside. Compounds designed to block the identified cellular interactions within the bone marrow microenvironment are expected to mobilise the leukaemic cells and make them more accessible to contemporary antileukaemic agents. The data provide novel insight into the pathobiology of BCP-ALL and indicate new therapeutic targets for patients.

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

The role of connective tissue growth factor (CTGF) in paediatric acute lymphoblastic leukaemia

UR Kees and J Ford in collaboration with MJ Firth, Division of Biostatistics and Genetic Epidemiology, and DR Brigstock, 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 B-cell precursor ALL (BCP- ALL) to normal CD34+ cells, and we identified a set of highly differentially expressed genes. Many of the top-ranked genes are known to mediate cell-cell interactions, including connective tissue growth factor (CTGF). Remarkably, four independent studies showed high expression of CTGF in about 75% of BCP-ALL specimens, while not present in T-cell ALL. Importantly, high CTGF expression is of prognostic significance as it is clearly linked to poor outcome, initially shown in adult patients, and recently demonstrated in a large study in high-risk paediatric patients. 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. The presence of rhCTGF enhanced adhesion of BCP-ALL cells to stromal cells. Contact to stromal cells led to resistance to drugs used in the therapy of ALL patients, including vincristine and cytosine arabinoside. These findings lead us to conclude that interactions within the bone marrow play a critical role in the development of BCP-ALL, and that secretion of CTGF initiates a cascade of events, contributing to leukaemogenesis and adhesion-mediated drug resistance. Improved understanding of the CTGF-mediated changes in pre-malignant and malignant cells 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.

CpG island methylation correlates with CTGF gene expression in paediatric acute lymphoblastic leukaemia

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

Our gene expression studies of B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) identified connective tissue growth factor (CTGF) as highly upregulated in the majority of cases. Immunoblotting confirmed secretion of CTGF in BCP-ALL cells and interestingly,

northern blotting revealed a novel variant of CTGF mRNA present in several CTGF positive cell lines, confirmed by sequencing of RACE products. CTGF is not normally expressed in B-cells or their progenitors and secretion of CTGF proteins appears to play a prominent role in ALL, leading to modified interactions with the microenvironment. In order to investigate the mechanism of high gene expression we analysed a panel of BCP-ALL cells by Southern blotting. This ruled out rearrangements affecting the CTGF locus. A combination of bisulfite sequencing and methylation-specific PCR identified epigenetic regulation of CTGF in the BCP-ALL cell lines. Demethylation of CpG dinucleotides across the CTGF CpG island was a feature of CTGF positive cell lines, while those lacking CTGF expression were hypermethylated at this locus. The study has now been extended to include primary patient specimens. Future experiments aim to examine the effect of pharmacological modulation of CpG methylation upon CTGF expression in vitro.

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

The role of connective tissue growth factor in haematopoiesis

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Perth, and KM Lyons, UCLA, Los Angeles, USA.

Haematopoietic stem cells (HSCs) are crucial in haematopoiesis and they reside in unique microenvironments or 'niches' created by bone marrow stroma, which is composed of fibroblasts, macrophages, endothelial cells, adipocytes, osteoblasts and osteoclasts. Although the balance of HSC self-renewal and differentiation is highly regulated by the integration of intrinsic factors with extrinsic cues from the surrounding microenvironment, little is known about these regulatory processes at the molecular level that is documented to include growth factors. Connective tissue growth factor (CTGF) is critical in bone formation and it plays a role in osteoblast proliferation and differentiation. Osteoblasts are known to regulate the fate of haematopoietic cells and produce many factors essential for the renewal and maturation of HSCs. Additionally, *Ctgf*^{-/-} mice showed multiple skeletal defects as well as impaired chondrocytes proliferation and they die shortly after birth, owing to respiratory failure caused by such defects. Our previous studies in B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) have demonstrated that CTGF was exceptionally upregulated in patient specimens. In order to directly test the role of CTGF in haematopoiesis, the *Ctgf*^{+/-} mouse strain was used to study haploinsufficiency. Examining B, T and myeloid cell populations in bone marrow, spleen, thymus and lymph nodes using flow cytometry identified no abnormalities. However, *Ctgf*^{-/-} newborn liver cells

showed an increased B-cell population and decreased myeloid population compared to *Ctgf*^{+/-} and *Ctgf*^{+/+} newborn liver cells. These findings suggest that CTGF appears to play a role in normal haematopoiesis and transplantation studies are in progress to elucidate the precise mechanisms.

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

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

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

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

of relapse in independent cohorts and across different experimental platforms. Using HG-UI 33Plus2 microarrays we modelled a five-gene classifier (5-GC) that accurately predicted clinical outcome in a cohort of 50 T-ALL patients. The 5-GC was further tested against three independent cohorts of T-ALL patients, using either qRT-PCR or microarray gene expression, and could predict patients with significantly adverse clinical outcome in each. The 5-GC featured the interleukin-7 receptor (IL-7R), low-expression of which was independently predictive of relapse in T-ALL patients. In T-ALL cell lines, low IL-7R expression was correlated with diminished growth response to IL-7 and enhanced glucocorticoid resistance. Analysis of biological pathways identified the NF- κ B and WNT pathways, and the cell adhesion receptor family, particularly integrins, as being predictive of relapse. Outcome modelling using genes from these pathways identified patients with significantly worse relapse-free survival in each T-ALL cohort. We have therefore used two different approaches to identify, for the first time, robust gene signatures that can successfully discriminate relapse and continuous complete remission patients at the time of diagnosis across multiple patient cohorts and platforms. Such genes and pathways represent markers for improved patient risk stratification and potential targets for novel T-ALL therapies.

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

Models of drug-resistance to predict patient outcome in acute lymphoblastic leukaemia

AH Beesley and UR Kees in collaboration with RA O'Leary and MJ Firth, Division of Biostatistics and Genetic Epidemiology.

Children with acute lymphoblastic leukaemia (ALL) are treated with complex chemotherapy regimens of up to ten different drugs according to risk stratification at diagnosis. Around 80% of patients achieve continuous complete remission (CCR) with early response to drug therapy being one of the strongest predictors of outcome. However a significant number of patients continue to relapse and for these the outlook is dismal due to the development of drug-resistance. Identifying potential markers of drug-resistance could improve patient stratification and further improve cure rates. Over the past 20 years our laboratory has developed a panel of paediatric ALL cell lines that retain critical features of the primary disease. Using the MTT viability assay we have measured the sensitivity of these cell lines to 13 commonly used ALL chemotherapeutic agents and have measured gene-expression profiles by Affymetrix HG-UI 33A microarray. In contrast to many of the cell lines that are available commercially, our cell lines generally grow at slow rates similar to the growth of leukaemic blasts in vivo. Their drug-resistance profile parallels the spectrum of resistance that has been observed in primary patient specimens, particularly in regard to dexamethasone.

We have correlated drug-resistance and gene-expression profiles to generate an extensive database of drug-gene signatures that are currently being analysed for biological function. Comparison of drug-gene signatures with the publicly available Connectivity Map has provided potential drug-leads that are under test in our laboratory. We are also in the process of developing a gene expression-algorithm based on our in vitro drug-gene resistance data that can predict outcome in primary patient specimens. The data was used to generate a model of predicted resistance scores that was subsequently assessed in microarray datasets from three independent T-cell ALL (T-ALL) patient cohorts. These scores were used to predict patient outcome (relapse or CCR) in each cohort. The top 50 genes correlating with in vitro resistance to each of the ten drugs were used in modelling. Using this model, relapse/CCR patient status could be predicted with >75% accuracy in each of the three independent cohorts. Predictions of relapse were driven by contributions from different drug combinations in each of the cohorts, indicating particular importance in T-ALL therapy. These findings demonstrate that biological pathways correlating to in vitro drug resistance may have prognostic potential in patients and highlight the importance of understanding how individual patients relapse. These genetic features contribute to our understanding of drug resistance and represent potential markers for improved patient stratification at diagnosis.

This work was supported by the

Children's Leukaemia and Cancer Research Foundation, WA.

Altered glucose metabolism in drug resistant paediatric T-lineage acute lymphoblastic leukaemia.

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

Despite significant improvements in the treatment of T-cell acute lymphoblastic leukaemia (T-ALL), as many as 20% of paediatric and 50-70% of adult patients develop treatment-resistant disease. Resistance to glucocorticoids (GC) is known to be a major factor contributing to the poor prognosis of relapsed ALL, however, the exact mechanisms remain to be elucidated. Our 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 signalling pathways. Importantly, the presence of these transcriptional signatures in primary ALL specimens significantly predicted patient outcome. Based on these findings we postulated that modulation of glucose metabolism pathways may be associated with drug resistance and evasion of apoptosis, thus we assessed whether GC-resistant cells increase their dependency on glycolysis. The bioenergetic phenotype was examined by in vitro assays, including measurement of cytotoxicity, ATP levels,

glucose consumption, lactate production and mitochondrial membrane potential. Cells were treated with inhibitors to glycolysis and oxidation phosphorylation, as well as chemotherapeutic agents to provide insights into the modulation of glucose metabolism and association with GC-sensitivity. Our data demonstrate that GC-resistance is associated with increased glucose consumption, lactate production and a glycolytic phenotype in T-ALL. Importantly, apoptosis was enhanced when T-ALL cells received a combined treatment of GCs and metabolic inhibitors, sensitising the cells to GCs. A higher mitochondrial membrane potential was found in GC resistant cells, suggesting a possible mechanism for the evasion of apoptosis and cell death. Understanding these bioenergetic mechanisms that underlie drug resistance in leukaemia is critical and is likely to lead to the identification of novel drug targets. Incorporation of selective metabolic inhibitors into current treatment regimens may improve treatment for drug-resistant leukaemia.

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

Influence of wild-type MLL on glucocorticoid sensitivity and response to DNA-damage in paediatric acute lymphoblastic leukaemia

AH Beesley, JL Rampellini, ML Palmer, JYS Heng, and UR Kees, in collaboration with MJ

Firth, Division of Biostatistics and Genetic Epidemiology.

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

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

Correlation of NOTCH1 activating mutations and sensitivity to 6-mercaptopurine in T-cell acute lymphoblastic leukaemia cell lines

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

Acute lymphoblastic leukaemia (ALL) is the most common cancer in children, with T-cell ALL (T-ALL) occurring in about 15% of cases. Using the current Children's Oncology Group protocol 5-year event free survival rates of over 80% have been achieved. However, for the patients that relapse many become resistant to the current chemotherapeutic drugs and a cure remains hard to achieve. NOTCH1, a critical developmental gene, was implicated in T-cell leukaemogenesis by the discovery of a t(7;9) translocation. More recently activating mutations of NOTCH1 have been demonstrated in over 50% of T-ALL patient specimens. Based on these observations we wished to (i) determine the mutational status of NOTCH1 in our unique panel of T-ALL cell lines and (ii) to correlate the presence of NOTCH1 activating mutations with the drug resistance profiles for these cells. DNA was extracted from 12 cell lines and NOTCH1 exons were PCR amplified and sequenced. Activating mutations of

the NOTCH1 gene were identified in 7 of the panel of 12 cell lines (58%). One cell line had a mutation in the juxtamembrane domain, three cell lines had a mutation in the heterodimerization domain only, and one cell line had a mutation in the PEST domain, whilst two cell lines had mutations in both the heterodimerization and PEST domains. The drug resistance profile of the T-ALL cell line panel for standard chemotherapeutic agents used in the clinic to treat T-ALL (including cytosine arabinoside, 6-mercaptopurine, 6-thioguanine, methotrexate, dexamethasone, methylprednisolone, daunorubicin, doxorubicin, L-asparaginase and vincristine) were then correlated to NOTCH1 mutation status. This revealed that cell lines with NOTCH1 activating mutations were more susceptible to 6-mercaptopurine and 6-thioguanine than cell lines without NOTCH1 activating mutations, indicating that they may be more important in T-ALL therapy than has been previously appreciated. These results have important implications for improved risk stratification and the development of individualised treatment strategies.

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

Novel drug therapy combinations for acute lymphoblastic leukaemia

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

The hallmark of therapy for paediatric patients with acute lymphoblastic

leukaemia (ALL) is the use of multiple drugs to avoid the development of resistance. Optimal therapy for patients with ALL should comprise drugs that effectively complement each other with respect to their mechanism of action and have a minimal effect on normal cells. Ultimately a paradigm shift is required to arrive at a combination of drugs that is necessary and sufficient to cure ALL patients, and such drug combinations may in the future be tailored to each patient. The current multi-agent protocols are very successful and they invariably include steroid drugs, which induce apoptosis in lymphoid malignancies but not in others. Despite their major impact on clinical outcome, studies of relapsed ALL have clearly demonstrated that resistance to steroids is the most prominent feature compared to all other drugs and new ways to tackle this problem are required. Importantly, our recent studies in ALL cell lines have revealed that the novel agent flavopiridol (FP) is highly effective in steroid-resistant cells. FP when administered in a pharmacologically-derived schedule in adults and children has been shown to achieve marked clinical efficacy in refractory haematopoietic malignancies, including acute leukaemias and relapsed high-risk chronic lymphoblastic leukaemia (CLL). Liposomes containing FP have recently been produced and this formulation has achieved significantly improved pharmacokinetics. However, the evidence that development of steroid resistance in ALL contributes to relapse makes it highly likely that clinical

resistance to FP would also ultimately evolve, as has been the case for the drug Gleevec. The objectives of this on-going study are to study the biological actions of FP and to derive FP-resistant ALL cell lines with which to investigate potential mechanisms of FP-resistance before the phenomenon is known in the clinic. This knowledge will contribute to the application of this novel therapy to the treatment of drug-resistant ALL.

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

Validation of a mouse xenograft model system for gene expression analysis of human acute lymphoblastic leukaemia

AL Samuels, VK O'Driscoll, AH Beesley and UR Kees in collaboration with MJ Firth and RW Francis, Division of Biostatistics and Genetic Epidemiology, RA Papa and RB Lock, Children's Cancer Institute Australia, Sydney.

Pre-clinical models that effectively recapitulate human disease are critical for expanding our knowledge of cancer biology and drug resistance mechanisms. For haematological malignancies, the non-obese diabetic/severe combined immunodeficient (NOD/SCID) mouse is one of the most successful models to study paediatric acute lymphoblastic leukaemia (ALL). However, for this model to be effective for studying engraftment and therapy responses at the whole genome level, careful molecular characterisation

is essential. We sought to validate species-specific gene expression profiling in the high-engraftment continuous ALL NOD/SCID xenograft. Using the human Affymetrix whole transcript platform we analysed transcriptional profiles from engrafted tissues without prior cell separation of mouse cells and found it to return highly reproducible profiles in xenografts from individual mice. The model was further tested with experimental mixtures of human and mouse cells, demonstrating that the presence of mouse cells does not significantly skew expression profiles when xenografts contain 90% or more human cells. In addition, we have developed a novel in silico and experimental masking approach to identify probes and transcript clusters susceptible to cross-species hybridisation. We demonstrated that species-specific transcriptional profiles can be obtained from xenografts when high levels of engraftment are achieved or with the application of transcript cluster masks. Importantly, this masking approach can be applied and adapted to other xenograft models where tissue infiltration is lower. This model provides a powerful platform for identifying genes and pathways associated with ALL disease progression and response to therapy in vivo.

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

A preclinical model of relapse in acute lymphoblastic leukaemia

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

Despite significant improvements in the treatment of childhood T-cell acute lymphoblastic leukaemia (T-ALL), up to 20% of patients relapse with most facing a dismal prognosis. Understanding the genetic mechanisms underlying the development of drug resistance in T-ALL is critical and will likely provide novel drug targets. Due to limitations associated with primary patient material, relevant pre-clinical models able to recapitulate human disease are essential. The non-obese diabetic/severe combined immunodeficient (NOD/SCID) mouse model provides a powerful platform to study paediatric ALL. Leukaemia cells engrafted into NOD/SCID mice retain the patient's phenotypic and genotypic features and mirror drug resistance profiles. To provide insight into mechanisms associated with relapse we have used the continuous ALL xenograft model to analyse drug resistance phenotypes in vivo.

Continuous xenografts were established from paediatric T-ALL patients at diagnosis in NOD/SCID mice. To represent a clinically relevant paediatric model we developed a 4-drug-treatment regimen to mimic remission induction therapy. Each xenograft was treated with a combination of vincristine, dexamethasone, L-asparaginase and daunorubicin (VXLD)

or vehicle control. To monitor the in vivo selection of therapy-resistant clones, we compared drug responses between control and treatment groups ex vivo, following relapse. Importantly, individual xenografts demonstrated therapy resistance to at least one of the four drugs administered. We have compared microarray gene expression profiles of the in vivo drug-selected T-ALL xenografts with their vehicle-treated controls and the original primary patient specimens. Ultimately, this study will allow us to answer fundamental questions regarding molecular pathways deregulated by the development of drug resistance in vivo.

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

The role of class IA aldehyde dehydrogenase (ALDH1A) retinoic acid-synthesizing enzymes in T-cell acute lymphoblastic leukaemia (T-ALL)

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

Several T-ALL oncogenes are known, of which two, TLX1/HOX11 and SCL/TAL1 are deregulated in over 50% of T-ALLs. These genes encode transcription factors and are thought to represent critical first-hit events, resulting in the emergence of pre-leukaemic T-cells with altered self-renewal and/or survival

capabilities. ALDH1A genes, which encode enzymes responsible for retinoic acid (RA) synthesis, have been identified as being downstream of both TLX1 and SCL and are frequently expressed in T-ALL, but not in normal thymocytes. Enforced expression of an ALDH1A gene can perturb both T-cell differentiation and haematopoiesis in general. Moreover, it has been well documented that RA is stimulatory to T-cell growth and survival. We therefore hypothesise that aberrant synthesis of RA may play a crucial role in the pre-leukaemic immortalization of thymocytes and/or maintenance of the T-ALL phenotype.

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

This work was supported by the Cancer Council of WA and the Children's

Leukaemia and Cancer Research Foundation, WA.

Metabolic analysis of glucocorticoid resistance in T-cell acute lymphoblastic leukaemia (T-ALL)

AL Samuels and UR Kees in collaboration with MJ Firth, RW Francis and K Carter, Division of Biostatistics and Genetic Epidemiology.

Despite significant improvements in the treatment of childhood T-ALL, as many as 20% of patients will relapse and most of those face a dismal prognosis. Resistance to glucocorticoids is known to be a major factor contributing to the poor prognosis of relapsed ALL, however, it is still unclear how patients develop resistance and which pathways are deregulated. Recent studies in our laboratory identified that leukaemia cells resistant to glucocorticoids alter their central metabolism and enhance glucose catabolism. The aim of this study is to interrogate the leukaemia metabolome to identify metabolites associated with glucocorticoid resistance, conducted in collaboration with Metabolomics Australia. Using this novel metabolic profiling technique allows us to identify key metabolic changes that occur in glucocorticoid-resistant cells compared to sensitive cells. Understanding the metabolic mechanisms underlying the development of drug resistance in T-ALL is of critical importance for the identification of novel prognostic indicators and the development of more effective

antileukaemic drugs.

This work is supported by the Cancer Council of WA.

Carcinomas

Novel BRD4 translocation in undifferentiated carcinoma

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

Three 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 from disease 8 months after diagnosis. We generated cell line PER-624 from her cancer cells and have determined that they contain several karyotypic abnormalities, including t(6;19), t(1;18;7) and add(3). FISH experiments

using whole chromosome paints, BACs, sub-telomere and PCR probes were done to determine the exact nature of these karyotypic abnormalities. These studies have shown that in this case, although the translocation involves chromosomes 6 and 19, BRD4 and a region of 19p were cryptically inserted into chromosome 15, co-localising next to the NUT gene. RT-PCR has confirmed that NUT is expressed in this cancer; however, Southern blot experiments indicate that the breakpoint is not in the same location as has been described in previous cases. PCR based experiments are currently being conducted to confirm the exact location of the breakpoint in this case. We are also undertaking a transcriptome analysis of the cell line. The sequencing has been completed by AGRF and the analysis of this data is underway.

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

Paediatric Brain Tumours

The identification of deregulated genes and pathways involved in the pathogenesis of primitive neuroectodermal tumours of the central nervous system.

CM Bertram, DJ Holthouse, L Genovesi, S Wong, PI Fuller, UR Kees, NG Gottardo, and PB Dallas.

Primitive neuroectodermal tumours of

the central nervous system (CNS-PNETs) are the most common type of paediatric brain tumour. 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 patient and family. The relatively poor outlook for children with brain tumours can be largely explained by the fact that the molecular pathogenesis of CNS-PNETs is only partially understood. The main priority of the brain tumour research program is to address this problem, and ultimately develop safer and more effective drugs and treatment strategies that are urgently required. To achieve this goal we are employing a variety of approaches to investigate the molecular biology of CNS-PNETs.

A subset of CNS-PNETs is 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, self-renewal and differentiation. As part of our approach to identifying the genes that regulate these pathways, we have analysed chromosomal aberrations in a panel of CNS-PNET cell lines using cytogenetic analysis, 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 CNS-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. Ingenuity Pathway Analysis (IPA) revealed predominant cell cycle up-regulation in CD133+ NSCs relative to MB which is likely to reflect the high proliferation rates of these cells associated with in vitro cultivation prior to expression profiling. In contrast, up-regulated neurogenesis and neurodevelopment pathways were prominent in comparisons of MB with foetal germinal matrix and CD133- neural progenitor cells. Several genes, including the zinc finger transcription factor ZIC1 and the putative oncogene MINA53, were significantly up regulated in MB compared to all control cell types. The functional significance of deregulated expression of these and other genes identified using this approach is being explored using an adenovirus-mediated manipulation of gene expression in NSCs. This system is expected to provide new insight into the link between deregulated NSC growth and MB pathogenesis, which will ultimately facilitate the design of more effective drugs and treatment

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

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

CM Bertram, S Egli, S Wong, PI Fuller, UR Kees, NG Gottardo and PB Dallas in collaboration with SM Hawes and G Peh of the Monash Immunology and Stem Cell Laboratory, and M Dottori of the University of Melbourne.

Human embryonic stem cell derived neural stem cells (hESC-NSCs) are an attractive cell type for studying aspects of brain development and tumorigenesis. To develop the full potential of this model system it is important to establish a reliable methodology for the manipulation of gene expression in hNSCs. To address this issue, we used an adenoviral vector with a CMV promoter driven green fluorescent protein (GFP) reporter gene (Ad5-GFP). We optimized conditions for Ad5-GFP infection and assessed the efficiency of infection of whole and dissociated ESC derived neurospheres, as well as the effect of adenoviral vectors on cell surface marker expression, proliferation and differentiation potential. Our results demonstrated that most neurosphere cells (~70%) express the coxsackie and adenovirus receptor and can be infected with Ad5. More specifically, the CD133+ hESC-NSC population could be infected more efficiently than the CD133- population and both populations expressed

GFP at high levels after infection. At low multiplicity of infection (MOI<25) the virus had no significant effect on stem cell marker expression (CD133 and Nestin), cell survival, cell proliferation rate or differentiation potential. This model system provides a practical new approach to study the link between deregulated NSCs growth and CNS-PNET pathogenesis.

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

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

PB Dallas, DJ Holthouse, L Genovesi, S Wong, 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 was supported by the NHMRC, Australia and John Lillie Fellowship (PBD).

The characterisation of deregulated microRNA expression in paediatric brain tumours

L Genovesi, S Wong, K Carter, and PB Dallas in collaboration with KM Giles of the Western Australian Institute for Medical Research, Perth.

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

significant role in the pathogenesis of CNS-PNETs. To address this issue in more detail we analysed the expression levels of a panel of 754 miRNAs in CNS-PNET specimens and neural stem cells (NSCs) using qRT-PCR in a low-density array format. We identified 31 up-regulated and 21 down-regulated miRNAs in primary specimens relative to NSCs. Interestingly, several of the over-expressed miRNAs were predicted to target FOXO1A raising the possibility that down-regulation of FOXO1A expression in CNS-PNETs may be linked to deregulated miRNA expression. We are currently investigating this possibility. We anticipate that the comparison and integration of mRNA and miRNA expression data from primary CNS-PNET specimens and NSCs will rationalise our understanding of the fundamental molecular mechanisms that initiate and maintain the brain tumour phenotype.

This work was supported by the Raine Medical Research Foundation and John Lillie Fellowship (PBD).

Development of a mouse ependymoma model

CL Burchill and NG Gottardo.

Ependymoma is the third most common brain tumour affecting children and remains incurable in 40% of patients. As is often the case with paediatric brain tumours, survivors are frequently left with devastating long-term neuro-cognitive sequelae. There is an urgent need for more

effective and safer therapies. Transgenic mouse tumour models are important tools to facilitate the study of tumour initiation and progression and are invaluable for pre-clinical studies. A genome-wide analysis of human ependymoma specimens demonstrated that all cerebral ependymomas exhibited activated NOTCH signalling and INK4A/ARF deletion and that radial glia (RG) were the putative cell of origin of ependymoma. Based on these observations we generated the first mouse model of ependymoma, which phenocopies the human disease precisely by over-expressing NOTCH1 in RG cells using the Blbp promoter and concurrently deleting Ink4a/Arf. However, the penetrance of ependymoma formation was low (1 to 5%) with a long latency (6 to 18 months), suggesting that additional genetic mutations are required for ependymoma formation, making the current model unsuitable for pre-clinical testing. A more extensive genomic analysis using high resolution SNP genotyping of a larger cohort of human ependymoma specimens (n=230) revealed frequent focal deletions in the tumour suppressor gene PTEN. Array comparative genomic hybridisation analysis of mouse ependymomas demonstrated numerous large chromosomal copy number alterations (CAN) as well as focal CAN, common to all tumours, which included the Pten locus. Thus, to more faithfully recapitulate the human disease, we are modifying the existing ependymoma mouse model by additionally deleting Pten. The development of such a model will be an important tool to enhance

our understanding of the biology of this disease and facilitate pre-clinical studies of novel targeted therapies.

This work was supported by the John Lillie Fellowship (NGG).

Drug sensitivity profiling of CNS-PNET cell lines

CL Burchill, CM Bertram, PI Fuller, PB Dallas, and NG Gottardo.

The effectiveness of conventional chemotherapy for the treatment of CNS-PNET patients has reached a plateau and treatment related sequelae remain a significant problem. The development of more effective and less toxic therapies are urgently required for children suffering from this disease. In an effort to address this issue, we are generating the drug sensitivity profiles of our unique panel of CNS-PNET cell lines which were established from primary patient specimens obtained locally. Commonly used chemotherapy agents such as vincristine and cisplatin are being tested in these brain tumour cell lines to determine their sensitivity and resistance profiles. Results obtained from these profiles will then be utilized as a foundation to ultimately test new therapies in vivo via developing a novel, pre-clinical intracranial orthotopic xenograft mouse model that best represents the disease in children.

Staff and Students

Head of Division

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

Research Staff

Alex H Beesley, PhD, Adjunct Senior Lecturer UWA

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

Nicholas Gottardo, MB ChB FRACP (Paeds.) PhD, John Lillie Fellow

Wayne K Greene, PhD, Senior Lecturer Murdoch University

Jette Ford, BAppSc, Grad Dip Comp

Amy Samuels, PhD, BSc (Hons)

Katherine Thompson, PhD, Bsc (Hons)

Jasmin YS Heng, BSc (Hons)

Sarah Wong, BSc (Hons)

Violet O'Driscoll, BSc (Hons)

Brooke Longville, BSc (Hons)

Chantel Burchill, BSc (Hons)

Paula Fuller, BSc (Hons)

Emmanuela Ferrari, BSc (Hons)

Postgraduate Students

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

Cornelia Bertram, MBs, PhD candidate

Mathew Welch, BSc (Hons), PhD candidate

Laura Genovesi, BSc (Hons), PhD candidate

Laurence Cheung, BSc (Hons), PhD candidate

Ashley Schoof, BSc Honours candidate

Research Support

Stewart Cattach

Administrative Support

Joanne Graham

Theses passed

Ashley D. Schoof BSc Honours degree. "NOTCH1 activating mutations are correlated with increased sensitivity to 6-mercaptopurine in T-cell acute lymphoblastic leukaemia cell lines." (Supervisors U.R. Kees, J. Jago and N.G. Gottardo)

External Committees

International

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

National

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

Peter Dallas and Nicholas Gottardo. Australian Children's Clinical Trials Group.

Regional

Ursula Kees. Cancer Council of Western Australia

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

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

Invited Presentations

Beesley AH, Firth MJ, O'Leary R, Kees UR (2009). Prediction of disease outcome in paediatric acute lymphoblastic leukaemia through modelling of in vitro derived drug-gene profiles. WA Cancer Council Research Symposium, Perth.

Beesley AH (2009). Genetic fingerprinting for improved outcomes in paediatric

leukaemia. Tumour Immunology Group Research Forum, Perth.

Dallas PB (2009). A human neural stem cell model for the study of the pathogenesis of paediatric brain tumours. Cancer Council of WA Symposium, Perth WA.

Dallas PB (2009). A human neural stem cell model for the study of the pathogenesis of paediatric brain tumours. Australian Society for Stem Cell Research, Annual Meeting, Canberra ACT

Gottardo, NG (2009). Concurrent activation of NOTCH cell signalling and deletion of INK_a/ARF in radial glia causes cerebral ependymoma. Australian Society for Stem Cell Research, Annual Meeting, Canberra ACT

Kees UR (2009). The next big step in children's cancer research: the goal and the reality. Perspectives in Child Health, Telethon Institute for Child Health Research, Perth.

Kees, UR (2009). Gene expression profiling in paediatric acute lymphoblastic leukaemia: insights into pathogenesis and therapy resistance. Cancer Research Day, Murdoch Children's Research Institute, Melbourne.

Details of research Funding awarded in 2009

Children's Leukaemia and Cancer Research Foundation (CLCRF) Grant (2009 - 2012): 'Therapy for steroid-resistant paediatric

acute lymphoblastic leukaemia' (Kees UR, \$1,247,671 over 3 years).

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

Cancer Council WA Project Grant (2009 – 2010): "The role of retinoic acid-synthesising enzymes aldehyde dehydrogenase (ALDH) 1A1 and 1A2 in T-cell acute lymphoblastic leukaemia" (WK Greene and UR Kees, \$140,000 over 2 years).

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

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

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

Raine Priming Grant (2008-2009): 'The characterisation of deregulated microRNA expression in paediatric brain tumours' (P Dallas, \$170,000).

Molecular Biotechnology

Overview

Previous work of the Division of Molecular Biotechnology has identified the molecular nature of the house dust mite allergens and determined their IgE-binding hierarchy. Investigations in this area can now be conducted with pure allergens in known and reproducible doses and new prognostic and therapeutic reagents can be developed. Work continuing in this vein with cat allergy has identified the Fel d 7 and Fel d 8 allergens, which are more important than the Fel d 1 allergen for a significant number of cat-allergic individuals. It has however also been demonstrated that neither the size of IgE responses to allergens or the complexity of the allergen recognition can predict the manifestation of asthma. As described below some of this is explained by reduced IgG antibodies in subjects that experience frequent and persistent disease but the cause of this needs to be determined. A study initiated to determine how respiratory allergy affects responses to other mucosal antigens has shown both altered and developmentally delayed IgG antibody responses of children to the protein antigens of the ubiquitous mucosal colonising bacteria *Haemophilus influenzae* and *Streptococcus pneumoniae*. This precedes the development of allergy and provides an avenue to investigate underlying differences in the immune system of children who become allergic. These studies are being undertaken with well-defined recombinant antigens that represent outer membrane proteins that are targets for protective immunity. A

similar strategy has now been initiated with rhinovirus to develop similar reagents for the highly antigenic VPI capsid antigen of rhinovirus. People also produce IgE antibodies to protein antigens of bacteria, which in allergic subjects increase during convalescence from asthma exacerbations. This has provided an intriguing new area of investigation since the ability of people to produce IgE to the different antigens of different bacteria is highly correlated and for atopic children the titre of the antibodies is paradoxically a protective risk factor for asthma.

Anti-allergen and anti-microbial antibody responses in frequent and persistent asthma

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 clinical history of children admitted to a hospital emergency department for asthma exacerbation was used to classify their disease into intermittent and frequent and persistent asthma. The IgE antibody titres to the house dust mite allergens that did not differ between the groups but the children with frequent and frequent and persistent asthma had lower IgG1 and IgG4 titres than children with intermittent disease. These in turn were lower than the titres found in house dust mite allergic children recruited from the general population. The IgG1 antibody titres to

the P6 outer membrane protein of the mucosal colonising bacteria *Haemophilus influenzae* was also the lowest in the children with frequent and frequent and persistent asthma. This indicates an overall deficiency in IgG production to mucosally-presented antigens.

Developmental delays in anti-bacterial IgG antibody responses in the development of allergy

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

Initial studies showed that 2-year old children who became allergic at 5 years of age had an 85% decrease in the IgG1 antibody titres to the protective P6 antigen of the mucosal colonising bacteria *Haemophilus influenzae*. More extensive time course studies with the PspC and PspA family of antigens of *Streptococcus pneumoniae* and the P4 and P6 outer membrane protein antigens of *H. influenzae* show a wide ranging defect. Decreased responses to the P4 antigen were evident at 2 years but recovered while the defect found for P6 antigen remained at least until 5 years of age. The responses to the PspC antigen of *S. pneumoniae* were decreased at 2 years, which was when they first appeared in children who remained healthy, and similarly the antibodies to PspA antigens were deficient when they first became significantly elevated at 3 years of age. There is accordingly an overall delay in

the development of the IgG1 antibody to protein antigens of the common colonising bacteria of the respiratory mucosa. Since most children do not show skin test reactivity or IgE anti-allergen antibodies at this early age the defective IgG responses precede allergic sensitisation.

The paradoxical IgE responses to bacterial antigens

B.J. Hales L. J. Pearce, L. A. Hazell, Y.L. Chai, W. R. Thomas with P.G Holt, E.M. Hollams, F. Parsons. Cell Biology

IgE antibodies to the P6 outer membrane protein of *Haemophilus influenzae* were identified in about half of house-dust-mite-allergic asthmatics and were found to increase during convalescence from asthma exacerbation. Further study with antigens from *Haemophilus influenzae* (P4 and P6) and *Streptococcus pneumoniae* (PspC) showed that the same prevalence of IgE antibodies was found in sera from atopic and non-atopic children with the same baseline titres of about 1ng/ml to each antigen. IgE titres measured in the 1400 strong Raine cohort revealed two unexpected findings. The first was that the prevalence and titres of the responses to the different antigens were highly correlated showing an overall phenotype of IgE producers and non-IgE producers. The second was that among the atopic subjects, where the asthma rate is high, the presence of the anti-bacterial IgE was an independent negative risk factor and subjects with the highest IgE titres had the

lowest odds ratio for developing asthma.

Rhinovirus antigens

J. Iwasaki, W. Smith, W. R. Thomas, B. J. Hales

Rhinovirus infection frequently exacerbates asthma and may have a role in the development of allergic sensitisation. 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 accompanying immunopathological effects of infection are due to cross-reacting non-neutralising responses. The production of the highly antigenic VP1 capsid protein as a recombinant polypeptide has been undertaken so accurate measurements of isotype-specific antibodies and T-cell responses can be made. The VP1 proteins of members the type A, B and C families human rhinovirus are being made. Each has about 80% sequence identity within the family which is sufficient to measure cross reactive responses. The type C is a newly identified family that is especially associated with lower respiratory tract infection and asthma. It has not been possible to cultivate the type C virus so the production of the recombinant polypeptide is the only avenue available to measure immune responses and conduct seroepidemiology. DNA encoding the VP1 antigens has been obtained by gene synthesis and expressed in *E. coli*. The pattern has varied with the isolate. The type A protein is poorly expressed, the

type B can be produced in high yield as a soluble protein and a type C isolate has been produced in good yield in inclusion bodies. Expression of other isolates, especially for the type A are being undertaken as well as downstream purification.

Fel d 7 and Fel d 8 allergens of the cat

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

It is known that there are several allergens in cat extracts that bind IgE from cat subjects at mid to high frequency. The knowledge of these proteins is however insufficient to determine if they make important contributions to the allergic responses to some or all cat allergic subjects. Published information from the cat genome project at the US National Cancer Institute and molecular cloning has been used to produce recombinant Fel d 7 and Fel d 8 allergens. Fel d 7 is a salivary von Ebner gland protein similar to the major allergen of dogs and Fel d 8 is a protein similar to the surfactant-like latherin protein found in the skin and saliva of horses. Antibodies to the Fel d 7 allergen cross-reacted with the dog allergen for some sera and not for others. The allergen could be detected in high concentration in saliva. Both Fel d 7 and Fel d 8 bound IgE in the sera of over 40% of cat allergic subjects and for each allergen about 10% of cat-allergic subjects

had significant and higher IgE binding than that to the major Fel d 1 allergen. These results along with previous information on Fel d 2 and Fel d 4 show that while Fel d 1 is the overall major allergen, a significant minority of cat-allergic people have their highest response to another allergen and the titre can be high.

Stimulation of responses to bystander antigens by cysteine protease allergens

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

Evidence is not only accumulating to show that allergic responses to dominant allergens augment responses to other allergens presented at the time but also that they have intrinsic adjuvant properties that are important for this process. A mouse model of inhalation allergy to the cysteine protease allergens has been used to examine how their enzymatic activity, which is also found in the dominant Der p 1 allergen, might mediate these activities. It was shown that intranasal administration of the activated enzymes papain and ficin without adjuvant did induce persistent and boostable IgE antibody and Th2 type lung inflammatory responses that were dependent on the enzymatic activity. Similarly activated but not inactivated enzymes produce increased and more prolonged responses to the bystander Der p 2. Since the immune responses to the different cysteine protease allergens

were found to vary amongst mouse strains in an MHC dependent manner it was possible to determine if only protease activity was required. The bystander effect in different mouse strains showed that the bystander stimulation was only elicited in mice that also responded well to the cysteine protease allergen. The adjuvant activity for the bystander responses was therefore not directly mediated by protease activity.

Staff and Students

Research Staff

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

Paula Cunningham PhD

Belinda Hales PhD

Tatjana Heinrich PhD

Wendy-Anne Smith PhD

Tracey Chai BSc (Hons)

Claire Elliot BSc (Hons)

Lee Hazell Dip Appl Sci

Postgraduate Students

Sarah See BSc (Hons)

Ashraf Sharafi BSc (Hons) MSc

External Committees.

W. R. Thomas. International Allergen Nomenclature Committee

Population Sciences

Overview

The Division of Population Sciences is the biggest Division at the Institute, consisting of almost 200 staff and students in multidisciplinary teams made up of epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists. 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.

Research interests of the Division include the investigation of a wide range of burdensome conditions; in particular those that affect the developmental health of children including low birth weight, behavioural and mental health problems, autism, obesity and infection.

Research methods utilized by divisional researchers range from quantitative methods involving linked population databases to identify patterns and trends of morbidity and mortality; as well as developing innovative ways of measuring and analysing the important influences in whole populations of children, their families and communities; to qualitative methods involving participatory action research, focus groups and the exploration of the views and perceptions of community members in response to specific issues.

The Division maintains a preventive focus in all its research that aims to promote and maintain the health and development of children, as well as supporting and

enhancing their social, emotional, academic, and vocational wellbeing.

Highlights for 2009

1. In January 2009, our researchers revealed the consequences of heavy and binge drinking on pregnancy even after these drinking patterns have stopped. The study investigated the relationship between prenatal exposure to alcohol and the effects on fetal growth and preterm birth. The researchers found adverse effects of high alcohol use that demonstrates heavy and binge levels of alcohol during pregnancy increases the risk to the baby, even if drinking is stopped in the first three months of pregnancy. The results did show that low levels of alcohol consumption (less than 7 standard drinks per week and no more than two on any one occasion) appeared not to constitute a significant risk of preterm birth provided all other forms of unhealthy behaviour such as smoking were avoided. This study provides some insight into the drinking habits of a representative group of women warning that the combination of smoking and heavy drinking can mean double trouble for pregnant mothers and their babies.

2. In February 2009, researchers within the Division were awarded a prestigious \$9.7 million grant to undertake an unprecedented program of research to determine the critical social, economic and environmental factors in pregnancy and early childhood that have a lifelong impact on health and wellbeing. The

work, funded by a program grant from the National Health and Medical Research Council (NHMRC), will be undertaken at the Telethon Institute for Child Health Research in collaboration with researchers from the University of Western Australia and Curtin University of Technology. The comprehensive research program will analyse trends and impact of developmental disorders and mental health problems in childhood and the extent to which they contribute to educational problems, child abuse and neglect and crime. It will also examine early childhood influences on an adult's later abilities and participation in the social, economic and civic aspects of our society. The NHMRC funding begins in 2010 and funds five years of research.

3. In May 2009, researchers within the Division found that twins born as a result of assisted reproductive technology (ART) such as IVF were more likely to be admitted to neonatal intensive care and to be hospitalised in their first three years of life than spontaneously conceived twins. The results were based on an analysis of hospital admissions for all twin children born in Western Australia between 1994 and 2000. The researchers found that twins conceived following ART treatment had a greater risk of preterm birth, low birthweight and death compared with spontaneously conceived twins. We don't know the reason for the increased risks of health problems and preliminary analysis of specific diagnoses does not provide any answers. More research is needed to establish whether it could be due to the

underlying causes of parental infertility and/or components of the ART procedure.

4. Also in May 2009, a new study by researchers within the Division showed the link between Western-style diets and more mental health problems in teenagers. The results were based on detailed analysis of diet records and behaviour checklists that were collected from more than 1600 West Australian 14-year-olds in the Raine Cohort Study. The analysis found that higher levels of behaviour and emotional problems were associated with a more Western-style way of eating, namely a diet high in takeaway foods, red meat, confectionery, soft drinks, white bread and unrefined cereals. It also showed that these problems were less among teens with a healthier style of eating, specifically those who ate more fruit and vegetables.

5. In July 2009, a link between healthy growth in the womb and improved numeracy and literacy skills in early primary school was revealed. The studies, published in the international Journal of Epidemiology and Community Health and American Journal of Epidemiology, showed that healthy fetal growth not only helps to improve a child's performance at school, but that it may contribute towards closing the achievement gap for children from disadvantaged socioeconomic backgrounds. The study was made possible through collaboration between the Institute and the WA Departments of Education and Training and Health that allowed the de-identified linking of midwife records and standardised testing (WALNA) results

Division name

from more than 55,000 children.

This research study represents the first time that the Division has been able to match birth and educational information and identify some of the broad factors that are linked to educational success.

6. Research into the issue of folate and birth defects has been one of the most exciting areas of research from the Institute where we have been able to show that the simple addition of a vitamin to the diet can prevent neural tube defects such as spina bifida. Over the years, researchers from the Division have worked with authorities in demonstrating the health value of fortification of flour with folate. In September 2009, the Food Standards Australia New Zealand (FSANZ) approved the mandatory fortification of bread making flour. This fortification will help to save hundreds of families from the heartbreak of serious birth defects.

7. In September 2009, new research from Division showed long term benefits for a child if their mother quits smoking even after the pregnancy is established. The study revealed that even if a woman is still smoking in the first few months of pregnancy, it is not too late to quit to improve the outcomes for her child. The analysis revealed an association between mothers who quit by 4 months gestation and a reduced risk of behavioural problems in the child. The analysis was drawn from data collected from more than 2800 participants in the Raine Study. Behaviour was assessed at 2, 5, 8, 10 and 14 years of age.

8. A study by researchers within the Division released in October 2009, found that the rapid increase in the number of children diagnosed with autism spectrum disorders (ASD) in Western Australia reflects changes to diagnostic practices and services. The study investigated factors behind the alarming increase in autism rates. The study found that in 1983 1.7 in every 10 000 children born in WA were diagnosed with ASD by age 8 compared with 53.4 per 10 000 children born in 1997, representing a 16.6% increase per annum. While we need to do more research to see if there is also a real increase in prevalence, we are confident that a substantial proportion of this rapid rise is due to better diagnosis and access to services.

9. In November 2009, a Divisional research project found evidence that the amount and timing of alcohol consumption in pregnancy affects child behaviour in different ways. The analysis was drawn from a random sample of more than 2000 mothers who completed a questionnaire three months after the baby's delivery, and were then followed up when the child was 2, 5 and 8 years of age. Mothers who reported what we would classify as heavy drinking in the first trimester of pregnancy were nearly three times as likely to report that their child suffered with anxiety and/or depression or somatic complaints. Exposure to moderate or heavy levels of alcohol in late pregnancy increased the risk of aggressive types of behaviours in the child. The research suggests that both the timing and the intensity of alcohol

exposure in the womb affect the type of behaviour problems expressed. In this study low levels of alcohol did not increase the risk of harm to the baby. However, the evidence clearly shows that the risk to the baby increases with increasing amounts consumed.

10. In December 2009, researchers within the Division found a possible association between parental occupations and a common birth defect which could warrant further investigation. This research found that mothers who may be exposed to heavy metals in their occupations were two and a half times more likely to have a son diagnosed with hypospadias, a common birth defect that affects the penis. Women working in the dental industry, defence forces, as laboratory workers and in petrol stations were identified as being potentially exposed to heavy metals. The study looked at the parents' occupations of more than 1200 boys with hypospadias and compared them with the occupations of the parents of more than 2500 boys without hypospadias. Potential exposure to 7 different types of (endocrine disrupting) chemicals was assessed for 348 parental occupations and then compared between cases and controls. Hypospadias is the second most common birth defect among boys in Western Australia, affecting about one in 130 boys. The rate has been increasing in recent years. Boys with the condition may have trouble urinating and fertility problems as adults. Hypospadias can be corrected with surgery.

Community Participation in Population Health Research

The Division of Population Sciences has supported a division-wide approach in 2009 to encourage greater consumer and community participation in the following ways:

Ongoing participation activities: research areas and projects such as Infectious Diseases, the Raine Study, Alcohol and Pregnancy and Rett Syndrome continued to maintain and support their consumer and community advisory groups and activities.

New activities: the Growth and Development Study established a reference group following a meeting with 25 interested community members. The Growth and Development Team decided to take advantage of technology and explored the use of blogs and Facebook to better engage with the reference group and community members.

Community Conversations: two research areas - Understanding Disability and the Raine Study were involved in the inaugural 'Community Conversations' held in June and August. The purpose of these conversations was for consumers and community members to learn about current research projects and identify gaps in the current work and priorities for future research. 44 consumer and community members attended the workshops. An immense amount of valuable and insightful information was gathered. This information will be used

to guide the development of future work in each of the areas. Funding for the 'Community Conversations' was generously provided by the Collaboration for Applied Research and Evaluation.

Input into grant applications: The Developmental Pathway Project used the 'Community Conversation' process to gain community input into developing research questions for a grant application. A workshop was held in October where researchers and community members discussed the current research projects and put forward new and innovative ideas for future work.

Research Training: 18 researchers from the Division attended pilot training workshops for researchers in April with researchers from the UWA School of Population Health. These workshops were co-facilitated by the Consumer Research Liaison Officer and a UK consumer advocate. The workshops were a direct response to researchers expressing a need for training and ongoing support to undertake consumer and community participation. The success of the pilot workshops led to a Summer School course being developed. Three researchers from the Division attended the two day workshops in December.

Interaction with the Consumer and Community Advisory Council: senior staff regularly attended the quarterly Council meetings to provide updates and seek input on Divisional activities.

Consumer and Community Participation Award: Jan Payne was the recipient of the inaugural Consumer and Community Advisory Council Award in December. Jan was recognised for her outstanding commitment to good practice principles of consumer and community participation both in her own research and for being a 'champion' in the Division.

The Division of Population Sciences continues to support and demonstrate leadership in increasing consumer and community participation in many of its activities. The new initiatives undertaken in 2009, such as researcher training and the community conversations has the Division well placed to continue achieving in all of its future research.

Capacity Building in Population and Indigenous Health

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

Investigators: Deborah Lehmann, Fiona Stanley, Sandra Eades, Nick de Klerk, Marisa Gilles, Dennis Gray, Ann Larson, Linda Slack-Smith, C Thompson, Charles Watson, Dawn Bessarab, Ngiare Brown, Juli Coffin, Janet Hammill, Jocelyn Jones, Cheryl Kickett-Tucker, Daniel McAullay, Ted Wilkes, Michael Wright.

Coordinator: Maude Walsh.

In collaboration with Curtin University (the grant holder), Combined Universities

Centre for Rural Health, University of Western Australia. The Indigenous Capacity Building Grant (ICBG) "Not Just Scholars but Leaders: Learning Circles in Indigenous Health Research" is a collaborative project that has its prime objectives:

1. 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 ICBG crosses the jurisdictions of Western Australia, New South Wales and Queensland by virtue of the location of the Aboriginal researchers supported by the grant.

The highlights of 2009 are:

- The award of Doctoral degree to Michael Wright
- Cheryl Kickett-Tucker appointed Associate Professor at Murdoch University
- Juli Coffin appointed Associate Professor

at the University of Western Australia

- co-hosting of a Racism roundtable leading to the 'Boatshed declaration' and submission to HREOC

- Development of an International Indigenous Health Unit at Curtin University

- Stakeholders Forum where Team Investigators presented their work

- Preparation and Launch of the Community Report

To date the key outputs of the Team Investigators on this Indigenous Capacity Building Grant are as follows:

- 9 books/book chapters
 - 35 journal publications; 10 first author
 - 14 substantial reports
 - 32 presentations at international conferences
 - 37 presentations at national conferences
 - Successful grants: 21 NHMRC (15 as chief investigators), 2 from ARC grants and 6 Healthway grants
 - Award of 2 PhDs (1 with distinction); 2 nearing completion; 1 to continue on another CBG
 - Appointment of 4 Associate Professors
 - 1 became a Member of the Order of Australia
 - 2 NHMRC post-doctoral fellowships
- Funders of the project: The ICBG is

primarily funded by the National Health and Medical Research Council (NHMRC Grant #: 323213) with support funding from Curtin University of Technology for the five year life of the grant.

Aboriginal Health Research

Kulunga Research Network

2009 has seen a transition in the direction and operations of the Network in both its personnel and the focus of its work since the last Annual Report. We have continued to progress all current projects as well building new relationships and future research which has created the opening to engage new team members who bring with them a cross section of experiences and background to their roles.

The new Team Members are:

Dr Kate Riddell has been engaged to take the lead role in the Rio Strong Foundations Strong Future Project. Kate joins us as a Senior Research Officer and holds a PhD in Political Science and International Relations from the University of Western Australia.

She worked as a Research Associate on a number of university research collaborations with state and federal government, including: 'Understanding Muslim Identities: From Perceived Relative Exclusion to Inclusion', and 'Countering Racism in Western Australian Public Schools.' She has also authored and co-authored a number of research and

conference papers, most recently a research paper on racism in public media discourse - 'Murderous Little Malcontents' - presented at the 2009 Australian Political Studies Association conference, and a report on findings from the Countering Racism project to the 2009 Ethnic and Communities Council Queensland Multicultural Summit. She has extensive teaching experience in Politics at UWA, and her experience in social inclusion/exclusion and racism research will be much valued in the Kulunga Team.

Francine Eades joins us as Senior Research Officer. She is a Senior Registered Nurse with extensive experience in the delivery of primary health care to Aboriginal, including as Health Service Manager at Derbarl Yerrigan Health Service. Francine has a Masters of Applied Epidemiology from the Australian National University, and has been involved in and facilitated a number of research projects, including: A Healthway funded smoking in pregnancy study, an NHMRC Happy Kids Project, and Bibbulung Gnarnep (Solid Kids). She has served on Aboriginal community reference groups and ethics committees, and worked with the Director of Nursing at RPH and the RPH GP Liaison Officer to establish an Aboriginal clinical nurse liaison. She was a Research Coordinator at the Telethon Institute of Child Health Research from 2000-2002, on the WA Aboriginal Child Health Survey.

Francine has worked to develop partnerships and collaborations to improve health care and outcomes for Aboriginal

people. She brings to the team extensive research experience and the value of her community level relationships is exceptional.

Josephine Maxted joins us as a Research Officer involved in the SFSF partnership, and the lead researcher on KRN's partnership with Alcoa. Josie is a nurse and holds a Bachelor of Social Work. She has worked in the health industry for 30 years and within the addictions area for the last 14 years. In 1992, she won the inaugural National Captain Reginald Saunders Scholarship to study addictions in Social Work. Josie is currently registered with the Australian Association of Social Workers and is highly involved in a number of State and National social work boards and committees, including the national Aboriginal Social Work Sub-Committee (AASW), and the Indigenous Social Work (WA) Meetings. In addition to this, Josie is the Vice Chairperson for Yorgum Aboriginal Counselling Service, which provides counselling for family violence and sexual abuse as well as the Emotional Social and Well Being – LINK UP Family Reunification service.

Josie is currently a member of the State Health Consumer Council, and served previously as a ministerially appointed community member to the Department of Premier and Cabinet's Community Safety and Crime Prevention Council. She is a valuable member of the KRN, bringing to it her years of research and community experience, as well as her commitment and dedication to improving the health

and wellbeing of Aboriginal people and communities.

Associate Professor Roz Walker has continued to work with Kulunga as a research consultant with Kulunga most notably on BHP Staying on Track project, the ACER Mental Health Textbook, the Australian Early Development Index (AEDI) and the Aboriginal AEDI projects described elsewhere in this report.

Terry Boyle and Carrington Shepherd were successful in securing scholarships and have commenced fulltime studies to undertake a PhD with Carrington still working with Kulunga on requests for the WA Aboriginal Child Health Survey data.

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

Glenn Pearson, Josie Maxted, Heather Monteiro, Carrington Shepherd, 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.

Work on this project over 2009 saw the results presented at two national forums and published in Tobacco Control with the drafting of a Memorandum of Understanding currently being finalised between Kulunga and the Cancer Council of WA. Additionally planning has commenced on future collaborative

research in 2010 to explore the factors contributing to Aboriginal smokers successfully quitting.

Funders of the project: The Cancer Council WA .

Rio Tinto Aboriginal Health Partnership – Strong Foundations, Sustainable Futures

Glenn Pearson, Kate Riddell, Josephine Maxted, Francine Eades, Jackie Goldfinch, Clair Scrine, Heather Monteiro, Tracey-Lee Edwards, Gail Barrow, Terry Boyle.

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

The RTAHP and SFSF have built on the outcomes and relationships developed during Rio Tinto Child Health Partnership (2002-2007) (RTCHP). In particular, the SFSF project arises out of the RTCHP findings on the critical role Aboriginal Health Workers in delivering health

services to Indigenous people, and on a range of workforce development issues identified by Aboriginal Health Workers.

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

The new project team has completed, or is near to completing, on the following key deliverables:

- Development, production and delivery of the Start Stronger, Live Longer health resource for Aboriginal Health Workers. The conceptual basis of the resource is 'health for life,' emphasizing the importance of a good start in life as foundational to a longer, healthier life. It focuses on seven key themes: Maternal Health and Wellbeing; Infant and Child (0-5) Wellbeing and Development; Adolescent Health and Wellbeing; Mental Health and Wellbeing; Nutrition and a Healthy Lifestyle; Smoking, Alcohol and other Drugs; and How to Do Health Promotion and Research.

- Delivery of training and roll out workshops in the key regions. Commencing on March 17 2010, these workshops will consist of expert training around key themes addressed in the health manual, as

well as walking Health Workers through the manual and demonstrating how the resource can be used in health education and promotion activities.

- Start Stronger, Live Longer National Health Worker Symposium. This event will be held on 8 and 9 June 2010 at the University of Western Australia Uni Club. The symposium program is organized around the themes of the resource manual, and will include key note speeches, plenary and breakout sessions. The symposium will give Aboriginal Health Workers the opportunity to learn, up-skill and network with experts and colleagues.

- Two scholarships were awarded for study in 2009. Lyn Cheedy completed her diploma in Aboriginal Health Work, graduating top of her class from Marr Mooditj Aboriginal Health Training College in November 2009. Sarina Morgan had to defer her Certificate 4 studies with Kimberley Aboriginal Medical Services School of Health Studies to 2010.

Funders of the project: Rio Tinto.

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

Glenn Pearson, Josie Maxted, Claire Scrine, 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 build the knowledge base regarding health status of Aboriginal communities and families 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).

Funders of the project: Alcoa Australia.

AHCWA Models of Excellence in Aboriginal Child and Maternal Health

In 2007 the Australian Department of Health and Ageing funded the Aboriginal Health Council of Western Australia (AHCWA) \$1m to increase the capacity of this sector to provide maternal and child health services for Aboriginal people within the WA Aboriginal Community Controlled Health Sector (ACCHS's).. This funding was specifically targeted to promote innovation and excellence in child and maternal health service delivery by Aboriginal Medical Services within Western Australia.

The delivery of high quality primary health care is key to supporting families to be healthy. The issue of maternal and child health is of great importance to parents in Aboriginal communities who know

that healthy babies can become healthy children and healthy adults. To achieve this, quality primary health care services are needed that provide access and excellence in service provision. Comprehensive primary health care with strong linkages to hospitals and outreach services make a difference to the health of women of child bearing ages, women during pregnancy, the foetus during growth and development, as well as children as they develop through infancy into childhood.

It was agreed that this funding be directed to build the capacity of those services that were already well established in this area and specifically those who would be considered models of excellence in child and maternal health service delivery.

Consequently three services were identified and assessed through a competitive funding process. These services are the Ord Valley Aboriginal Medical Service based in Kununurra, Mawarnkarra Health Service Aboriginal Corporation based in Roebourne and the Geraldton Regional Aboriginal Medical Service.

These services have used this funding to increase their capacity and to act as leaders within the sector to promote excellence in this area across all Aboriginal Medical Services.

Kulunga has already commenced planning to undertake further research through the three identified models of excellence sites which will see the staged implementation of a health intervention study in these sites.

Funders of the project: Department of Health and Ageing.

Treading Carefully: Socio political Implications of Genetic Research in Aboriginal and Torres Strait Islander Communities

Emma Kowal, Glenn Pearson.

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

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

Indigenous people who are participating in genetic research projects.

This project is a post doctoral research project being led by Dr Emma Kowal from the University of Melbourne.

Aboriginal Collaboration Council Advising on Research and Evaluation

Roz Walker, Patricia Walsh, Ashleigh Owen.

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

monitoring the effective implementation of Aboriginal research at TICHHR using a range of existing and new mechanisms and agreed criteria and priorities.

Key activities in 2009 include the appointment of a 0.2 FTE research and executive support for ACCARE to carry out its Terms of Reference; hosting of a Retreat on 30 September 2009 to determine and plan the future directions of the Council, research agenda priorities, expectations of Members and ACCARE's role within TICHHR. Subsequently a sub-committee was established to further develop ACCARE's advisory abilities; and ACCARE was formally endorsed as a sub-committee to TICHHR's Board. Throughout the year ACCARE met 8 times and provided advice and support to TICHHR DOH and Women's and Newborns' Health Network (WNHN) projects involving Aboriginal research; and advised and disseminated information on 10 other Aboriginal health projects that are of identified priority areas in closing the gap in Aboriginal health outcomes.

Funders of the project: Western Australian Department of Health.

Improved communication and informed decision making by Aboriginal families: Prenatal diagnosis, neonatal care, and end of life decisions'

Roz Walker.

This qualitative research aims to identify

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

This project will be completed by the end of May 2010 and will deliver the following outputs:

- A report including a literature review, findings and recommendations. A key finding is the need for cultural competence at system, organizational and individual practitioner levels. Cultural Competence audit tools have been developed to assist health professional in KEMH and PMH and will be trialed in 2010.
- Guidelines, pathways and protocols for health professionals to assist them to communicate effectively with Aboriginal families around issues in relation to prenatal, neonatal and end of life decisions.
- A resource kit to assist staff at KEMH (and other relevant hospitals) in understanding and working with an Aboriginal family to assist them to make decisions regarding their unborn or newborn child (or children).

- A culturally appropriate resource kit to assist Aboriginal and Torres Strait Islander families experiencing the death or dying of a child in making health care decisions for their child which take account of their family and community context.

Funders of the project: Western Australian Department of Health.

Factors associated with early onset of sexual activity in Aboriginal adolescents

Grant Smith.

This research project attempted to identify the causes and moderators involved in early onset of sexual activity; with a particular focus on Aboriginal communities. The present study found a distinct lack of research examining the factors predicting early onset of sexual intercourse in Aboriginal youth, and a lack of evaluation research determining the effectiveness of programs attempting to delay the onset of sexual activity in Aboriginal youth. However, based on the synthesis of the sparse Aboriginal-specific research with the non-Aboriginal specific literature and analysis of WA specific data from the Western Australian Child Health Survey, a number of factors have been identified as having potential relevance to intervention efforts aimed at delaying the onset of sexual activity in Aboriginal youth.

These include Individual-Level Factors (such as intent to engage in sexual activity, the normalisation of early sexual onset/

perception of peer behaviour; control, negotiation skills, aspirations, and self-esteem and self-affirmation); Family-Level Factors (lack of parental monitoring of child whereabouts and behaviours, positive parental attitudes toward early sexual onset, teenage pregnancy and marriage; Extra-Familial-Level Factors (peer behaviour, peer pressure and neighbourhood values/expectations; and Societal Factors (cultural patterns of sexual behaviour and cultural patterns of alcohol use).

Funders of the project: Western Australian Department of Health.

Audit of Antenatal Services for Aboriginal Women in WA

Tracy Reibel, Roz Walker.

The audit, initiated by the Women's and Newborn Health Network, has been undertaken to determine the extent to which antenatal services in Western Australia are utilised by Aboriginal women and to describe the characteristics of these services. This research project established which antenatal services currently integrate key service delivery factors considered in the literature to be responsive to Aboriginal women's needs.

Forty two government and non-government health services participated in the audit, however, only a small number (nine) were assessed as being consistent in meeting key indicators of cultural responsiveness, as well as demonstrating

a high level of routine antenatal care. The four key indicators of culturally responsive care used in analysis are: [1] the presence of an Aboriginal specific antenatal protocol; [2] confirmation of a specific program of antenatal care; [3] access optimised by location of service and availability of unbooked antenatal appointments and transport; and, [4] inclusion of Aboriginal Health Workers as members of multidisciplinary antenatal care teams. As these indicators are specific to antenatal care for Aboriginal women they establish baseline factors for culturally secure antenatal services. Cultural security is considered a solution to encouraging greater engagement by Aboriginal people in health services but does not replace consultation with Aboriginal women to further establish other elements of service delivery that address local needs and promote cultural security. Analysis of audit data has also provided an indication of the preparedness and capacity of health care providers and services to offer appropriate and effective care to Aboriginal women with an outcome that strongly suggests improvements are required.

The overall audit results, although involving estimates of average numbers of antenatal visits and client numbers, reveal a picture that is indicative of the degree of antenatal engagement in different services and health regions in Western Australia. The picture suggests that Aboriginal women are more likely to visit, and more often, a service that is primarily used by Aboriginal women and is in a community setting. This study demonstrates that many antenatal

services used by Aboriginal women have not achieved a model of service delivery consistent with the principles of culturally responsive and secure care. Analysis identified too few services that always incorporate Aboriginal specific antenatal protocols and maintain optimal access to ensure delivery of effective, culturally responsive antenatal care towards improved attendance and clinical outcomes. The implementation of culturally specific guidelines and allocation of resources and strategies to support staff and organisational cultural competence are recommended.

Funders of the project: Western Australian Department of Health.

Interim Targeted Contact Schedule for Aboriginal Children in Western Australia Project

Tracy Reibel.

This research project involved the compilation and analysis of existing literature and policies related to the Interim Targeted Contact Schedule for Aboriginal Children in Western Australia and used this to inform changes to the Interim Schedule for use with all vulnerable and at risk children while still acknowledging the specific needs of Aboriginal children. In other words, this report reviews the evidence base and provides for the development of an early years framework to inform a 0-5 years schedule of health services for vulnerable and at risk populations

within a universal continuum of care. There is consistent agreement that all families with newborn children initially require access to universal services which incorporate clear mechanisms for identifying risk and indicate pathways to appropriate referral / intervention which also includes access to culturally secure, integrated, comprehensive and targeted services where needed, supported by an appropriately resourced and skilled workforce. Across all state and territory jurisdictions, child health policies advocate a collaborative approach to service delivery with services being integrated or coordinated, ensuring appropriate services are offered and that there is continuity in the family journey across interdisciplinary and program boundaries. It is evident that the Interim Targeted Contact Schedule is aimed at providing a managed, evidence based and consistent approach to supporting Aboriginal families with newborns, providing guidelines to direct more intensive and targeted support to Aboriginal children and their families where this is required. What is less evident, however, is how integration with other services and agencies is supported or maintained and this is an area that requires further development. In summary, the Interim Targeted Contact Schedule, when considered within the context of current trends in child health service planning, includes early identification, detection and preventive strategies, appropriate multidisciplinary service delivery and incorporates key principles and indicators as noted in the literature. Further, the

development of a Vulnerable and at Risk Health Schedule similar to the Interim Targeted Contact Schedule; and the initiation of dedicated Vulnerable Families health teams to support the delivery of an intensive schedule to vulnerable and at risk families other than Aboriginal or refugee families; would complete the range of targeted service delivery for the early years in Western Australia. Combined with a clear centralised notification/referral system, this approach would increase the likelihood for vulnerable children to be identified at the earliest opportunity thus enabling intervention by support services to assist children and families. It is evident that a home visiting model represents the most effective engagement strategy for at risk or hard to reach families. It is imperative that any such system is clearly communicated to the range of agencies external to the Child and Adolescent Community Health as these agencies may be first point of contact for vulnerable or at risk infants.

Funders of the project: Western Australian Department of Health

Indigenous Mental Health Textbook

Roz Walker, Pat Dudgeon, Nola Purdie.

This project was a collaboration between the Australian Council for Education Research (ACER), Kulunga Research Network and Telethon Institute for Child Health Research. Dr Walker is an editor for 'Working Together - Aboriginal and Torres Strait Islander Mental Health and

Wellbeing, Principles and Practices', with Dr Nola Purdie, ACER and Associate Professor Pat Dudgeon, for Kulunga. The book which was completed in December 2009 explores culturally appropriate approaches to assessment and interventions for Aboriginal and Torres Strait Islander social and emotional well being and mental health issues. Thirty-eight Indigenous and non-Indigenous clinicians, cultural and educational experts from around Australia contributed to 21 chapters in the book.

The message by the Minister, the Hon Warren Snowdon MP, (Minister for Indigenous Health, Rural and Regional Health and Regional Services Delivery), describes the book as 'pioneering', 'an exciting new resource that will prepare students and practitioners across a range of allied health professions to meet Indigenous mental health needs when working in mainstream and Aboriginal Medical Services'. Similarly, Tom Calma, in his capacity as Aboriginal and Torres Strait Islander Commissioner for Social Justice states in the foreword that the book 'marks a watershed in the treatment of Indigenous mental health issues' and will 'stand to make an enormous contribution to the mental health of Indigenous Australians', as the chapters take account for our unique experiences of Aboriginal our communities.

This book will help the health workforce contribute to both the State and Australian Government's commitment to closing the life expectancy gap between Indigenous

and non-Indigenous Australians within a generation. It is an important contribution to the ongoing struggle for the achievement of health equality between Indigenous and non-Indigenous Australians. It offers new approaches to Indigenous mental health that simultaneously acknowledge the importance of cultural identity and resilience that exists as well as the pervasive effects of racism, and the disempowerment of colonisation and assimilationist policies. The book will enable practitioners to understand the historical and contemporary influences and social determinants on Indigenous social and emotional wellbeing and the impact on mental health policy directions. It will greatly assist all students of medicine, psychology and allied health and education to when working with Indigenous peoples in Australia.

The book incorporates specific clinical mental health assessment processes and culturally appropriate treatment interventions. Besides editing 21 chapters for this book A/Prof Roz Walker was the lead author of a chapter 'Working as a Culturally Competent Mental Health Practitioner and also co-authored three other important chapters with leading experts in areas related to the policy context, social determinants and assessment issues in Indigenous mental health. Several Institute research staff contributed to the book. Professor Steve Zubrick co-authored two chapters with Dr Roz Walker and colleagues – the policy context of Indigenous mental health and wellbeing and the social determinants

influencing Aboriginal and Torres Strait Social and Emotional Wellbeing. Two Aboriginal Team Investigators on the Indigenous Capacity Building Grant (ICGB) Dr Michael Wright and Associate Professor Ted Wilkes contributed to chapters on social and cultural contexts of Indigenous Mental Health and substance use respectively. Professor Sven Silburn completed a Chapter on Preventing Suicide in Indigenous populations. It is planned to disseminate the book widely to universities and training colleges throughout Australia in April or May 2010

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

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

Roz Walker, Ashleigh Owens.

The Staying on Track: Reducing Substance use/misuse among Aboriginal young people in the Pilbara commenced in October 2006 and was one of two projects funded through the BHP Billiton Iron Ore Health Partnership Agreement. It was completed at the end of 2009 although further funding may be sought in the future. The project lead, Dr Roz Walker utilised a participatory action research process with young people and key stakeholders in Newman, Hedland and surrounding communities to identify and develop innovative preventative programs to

address issues of substance use in these communities. Additional funding through the Criminal Property Confiscation 2002 Act was used to implement a range of interventions.

The three main aims were to:

1. Introduce specific BHP sponsored health related programs to reduce substance abuse among Aboriginal young people in Hedland and Newman and surrounds;
2. enhance the capacity of Aboriginal young people in Hedland and Newman; and,
3. partner with relevant government agencies and non-government organisations to improve access for Aboriginal young people to an appropriate range of health and well being services to achieve improvements in population health among Indigenous youth.

All of these aims were achieved during the life of the project through a range of early interventions and prevention initiatives to reduce substance misuse (including smoking, alcohol and illicit drugs use) in partnerships with key stakeholders including the Youth Involvement Centre, the Department of Indigenous Affairs (DIA) and the Department of Communities Stronger Families, and (ABHI) Healthy for Life program in Jigalong.

A suite of preventative and health promotion activities associated with the BHP BIO Staying on Track project aims were successfully undertaken, These

activities focuses on physical wellbeing; safe talk; enhanced self esteem, and positive messages; skills development and reducing boredom:

- The hip hop project (it covers ages 12-25 years);
- The Port Bound Festival Festival targeted to young people 12-25 years old (and their families), promoting positive youth and health messages, providing a drug, alcohol and smoke-free environment and useful information and resources and links to all relevant services for young people;
- The Hedland Youth Directory focusing on physical safety and wellbeing; empowerment and social involvement; interaction with stakeholders and access to information on services and resources (12-25 years);
- The Youth Involvement Council's (YIC) programs address key issues such as low self-esteem, dislocation from culture and country, lack of job aspirations and future goals, grief and loss, relationship and parenting issues, and enhancing decision-making skills;
- the Hedland Youth Leadership Council, promotes notions of ambassadorship and positive role models through a range of Leadership programs, youth groups in Hedland, Newman and surrounding communities; and
- The Swim for Life program supports and promotes the aspirations of young people and focuses on developing skills, esteem

and achievement; (15 – 20 years);

Throughout the implementation of the BHP Staying on Track project the team has utilised a community-based participatory action research approach to develop and implement a suite of preventative and early intervention strategies as part of the program.

This project was showcased at the National ARACY Think Tank on involving young people in research Sydney in November 2008 and the report published in 2009.

Walker, R., Turner, T., Todd, S., Clanton, S. & Murphy, R. 2009, 'Involving Young People in Research in Hedland - From ideas to action: a praxis model.' Chapter 13 in *Involving Children and Young People in Research. A Compendium of Papers and Reflections from a Think Tank for Research with Young People*. Co-hosted by the Australian Research Alliance for Children and Young People and The NSW Commission for Children. pp 145 -155.

Funders of the project: BHP Billiton Iron Ore Health Partnership 2006-2009 and Criminal Property Confiscations Act 2002 Funding 2008 -2009.

Evaluating the Halls Creek Mother Support Initiative

Roz Walker, Kate Muggliston, Valma Banks, Ailsa Munns.

'Yanan Ngurrangu Ngamayiu' is a home-visiting program for Aboriginal pregnant

women and parents of young children 0-3 years old which commenced in 2008. Experienced Aboriginal mothers and grandmothers are trained as community care workers to provide parents with support to improve, parental health behaviour and attitudes, and infant and child health outcomes through a range of culturally appropriate activities including home visiting. This project evaluation aims to assess whether and in what ways families and staff involved with the program believe that it has increased their level of self empowerment, knowledge and understanding of the importance of parenting roles and improved their health and wellbeing through the collection of participant stories. It aims to understand the extent to which the program is empowering for mothers and community care workers; improving health and development outcomes for children; and, enhancing social networks and communication between health care professionals and Aboriginal mothers and their families.

A qualitative method is being used to obtain Aboriginal mothers/carers and families, HCMSI staff and relevant stakeholders perspectives regarding the value and effectiveness of the program. This dialogic evaluative process helps to improve organisational learning, staff and participant empowerment and capacity as well as identify the things that work and the things that need to be addressed (Dart & Davies 2003). MSC stories have been collected from staff participants and 12 families, and discussions and semi-

structured interviews have been completed with several key relevant stakeholders in Halls Creek. The information reveals different perspectives, expectations and understandings of Aboriginal women and their families, community care workers and other health professionals and local stakeholders. A preliminary analysis of the MSC stories provides examples of how participation in the HCMSI for at least six months improves people's sense of empowerment, engagement with and access to health services and improvements in the health and social and emotional wellbeing of their children and families. Interviews with key stakeholders reveal the extent to which they hold different expectations of the program and are less clear about the benefits.

These stories highlight that program participants are encouraged and supported to: discuss their concerns about their roles, relationships, child development and other issues with community care workers and relevant others; further develop their relationship skills and community links; increase the quality and access to personal exchange opportunities; and, extend their social networks and quality of communication with significant others. Several participants talked of the differing expectations between the Department of Child Protection, the Police and the broader community regarding their role as a mother and their shift in understanding of the importance of their role in their family and the broader community since their involvement with the HCMSI. Some of the families have identified changes in

beliefs about parenting roles and greater understanding of using different ways to manage their children's behaviours and 'loving them up' more, the importance of good food and hygiene. Overall all of the stories collected suggest there is a positive program effect on maternal care. Several program participants interviewed have indicated that they feel that they can and should act in ways that will positively influence their child's development and /or behaviour.

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

Funders of the project: Western Australian Department of Health.

The ARACY Seeding Grant – Facilitating the Warburton Remote Community Consultation Process

Roz Walker, Ernest Stringer, Preston Thomas, Sven Silburn.

The team successfully obtained an ARACY seeding grant in November 2008 to facilitate an extensive consultation process with the Warburton remote community to address the poor education, health and wellbeing outcomes for children and young people in Warburton and throughout the Ngaanyatjarra lands. The complex reasons for the continuing disparity in outcomes is a pressing question with important policy and practice implications. Throughout 2009 representatives from the Ngaanyatjarra Council, Warburton School, Goldfields District Office and WA Department of Education, the Telethon Institute for Child Health Research and Curtin University participated in a community participatory action planning process. This partnership was successful in bringing together high level expertise; building on established relationships and engaging with the Warburton community - resulting in the development and submission of an ARC Linkage grant proposal in November 2009. Collaborations have been formalised between the Telethon Institute for Child Health Research, Curtin University, Menzies School of Health, and Melbourne University (through a PhD student as part

of the ARC linkage grant proposal. The Ngaanyatjarra Council contributed to all phases of the research from inception to implementation, communication, dissemination and monitoring and evaluation. Highlights of the consultation process include a national webinar, a seminar, and a workshop in Alice Springs. These activities provided highly valuable opportunities for communication between the multidisciplinary research team and the Warburton community and academic, local, state and Australian government sectors and non government and community agencies.

Four collaborative planning and review forums have proved highly productive in developing shared understandings and perspectives for undertaking the next phase of this participatory action research. The continued engagement of all partners has been and will continue to be essential to ensure the relevance of the research and its translation to policy and practice. Importantly, there is greater understanding of the importance of adopting culturally responsive consultation processes in remote Aboriginal communities. Commonly accepted practices -interviews, workshops, focus groups, community forums only work effectively once people have worked through their own family processes.

Other important outputs of collaboration include the establishment of a breakfast program, a proposal for a parents place, project update sheets and newsletters and community-led presentations. This project and the proposed ARC linkage grant, if

successful, will contribute to knowledge sharing between the research/academic, community and government/policy sectors, teachers and administrative staff in schools across the Lands. There are significant gaps in knowledge and evidence of promising practice in achieving academic outcomes in remote Australian Indigenous contexts. The team has undertaken a comprehensive literature review to identify evidence of the factors and interventions that improve Aboriginal academic outcomes including community/school partnerships.

In summary the key outcomes of this grant include the ongoing consultations between all partners and relevant stakeholders; presentations at local, state and the national levels involving Warburton community members, a literature review and the Round 2 ARC Linkage Grant

The effect of family-school partnerships on educational outcomes in a remote Aboriginal school: A pilot project. This proposed study if successful will describe and evaluate the impact of school-related activities by Aboriginal caregivers on the educational outcomes of schools in the Ngaanyatjarra lands. It will provide a significant body of evidence related to the effects of those interventions that will inform government policies addressing current national priorities seeking to identify strategies for assisting young Australians to achieve a healthy start to life. It will provide the basis for more effective government policies and programs, and information relevant to national priorities for programs that reduce the gap in educational and health

and wellbeing between Indigenous and non-Indigenous Australians.

Funders of the project: ARACY ARC/ NHMRC 'Future Generation' Research Network.

Birth Defects and Developmental Disorders

Alcohol and Pregnancy Resources for health professionals

Carol Bower, Elizabeth Elliott, Nadeine Henley, Anne Bartu, Jan Payne, Colleen O'Leary, Heather D'Antoine, Kathryn France, Raewyn Mutch.

The Alcohol and Pregnancy Project was funded from 2006-2008 by Healthway to develop and evaluate educational resources for health professionals about the prevention of prenatal alcohol exposure and Fetal Alcohol Spectrum Disorders. The resources (booklet, fact sheet, wallet cards for women and calendar) were distributed to over 3,500 Western Australian health professionals in 2007 and were subsequently evaluated. The evaluation showed that the resources were used by health professionals and had an impact on their practice; nearly half of them had changed or intended to change their practice in response to the resources.

We reviewed, revised and reprinted the resources in 2009 following the release of the Australian Guidelines to Reduce Health Risks from Drinking Alcohol

(NHMRC, 2009) and the booklet, fact sheet and wallet cards for women are available to download or order as hard copies from <http://www.ichr.uwa.edu.au/alcoholandpregnancy>. The resources are in great demand - we have distributed over 2,200 booklets, 4,000 fact sheets, and 16,500 wallet cards within six months of reprinting. The resources are reaching their target audience and have been ordered by organizations involved in Aboriginal health services, youth programs, drug service teams, corrective services, family services, and by professionals including paediatricians, obstetricians, medical officers, public health physicians, speech pathologists, psychologists, social workers, occupational therapists, policy officers, midwives, child health nurses, educators, and workforce development officers.

We have 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.

Funders of the project: NHMRC Program Grant #353514; NHMRC Fellowship #353628 (CB).

A new method of prenatal alcohol classification accounting for dose, pattern, and timing of exposure: Improving our ability to examine fetal effects from low to moderate exposure.

Colleen O'Leary, Natasha Nassar, Jennifer Kurinczuk, Carol Bower, Stephen Zubrick, Elizabeth Geelhoed.

The amount of alcohol necessary for fetal damage is unclear and it remains debatable whether there is a threshold level below which alcohol does not harm the fetus. Previous studies have used methods of classifying prenatal alcohol exposure that do not reflect real life maternal drinking patterns and are insensitive to the dose of alcohol consumed per occasion and the frequency of consumption, which affect the intensity of fetal alcohol exposure. Using data from the RASCALS longitudinal cohort we developed a new 'composite' method of classifying prenatal alcohol exposure to enable more detailed examination of the relationship between the dose, pattern, and timing of exposure and fetal/child outcomes. Importantly, the 'composite' method permits differentiation between low, moderate and binge patterns of drinking. Our research showed that previous methods of classifying maternal alcohol consumption which either averaged prenatal alcohol exposure or categorized exposure by quantity alone obscured the real pattern of drinking and led to some women who were actually drinking at heavy levels being classified in the lower dose category and vice versa. Using the

'composite' method, which more closely reflects real life drinking patterns, may avoid obscuring important relationships and reduce the likelihood of either over-stating or under-stating aspects of risk to the developing fetus.

Funders of the project: NHMRC Program Grant #353514; NHMRC Fellowship #353628 (CB).

Evidence of a complex association between dose, pattern, and timing of prenatal alcohol exposure and child behaviour problems.

Colleen O'Leary, Natasha Nassar, Stephen Zubrick, Jennifer Kurinczuk, Fiona Stanley, Carol Bower.

This project used data from the RASCALS longitudinal cohort to investigate the association between dose, pattern, and timing of prenatal alcohol exposure and child behaviour as measured by the Child Behaviour Checklist at 2, 5, and 8 years of age

The results did not find any association between low levels of prenatal alcohol and child behaviour problems. However, prenatal alcohol exposure at moderate and higher levels increased the odds of child behaviour problems with the dose, pattern, and timing of exposure affecting the type of behaviour problem expressed. Heavy alcohol exposure in first trimester increased the odds of internalizing behaviour problems almost three-fold, including anxiety and/or depression and

somatic complaints, while a moderate level of alcohol exposure in first trimester was associated with a two-fold increased odds of anxiety and/or depression. Late pregnancy (either second and/or third trimester) alcohol exposure increased the odds of aggressive behaviour. Moderate alcohol exposure increased the odds of aggressive behaviour by two-fold and heavy alcohol exposure by three-fold. Although low levels of alcohol exposure did not increase risk in this study, there were only subtle differences in relation to dose per occasion between the low and moderate classifications in this study. Therefore, the safest message for pregnant women is to abstain from alcohol.

Funders of the project: NHMRC Program Grant #353514; NHMRC Fellowship #353628 (CB).

Pregnancy outcomes following assisted reproductive technologies (ART)

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

Using record linkage, we investigated hospital admissions during the first 3 years of life for all twin children born in Western Australia between 1994 and 2000. The analysis was based on 700 ART infants and 4097 spontaneously conceived infants (1240 of which were non-identical twins of different sex). ART twins had a greater risk of adverse perinatal outcome including preterm birth, low birth weight

and death compared with spontaneously conceived twins of unlike-sex. In their first year of life, ART twins had a longer birth admission; were 60% more likely to be admitted to a NICU; and had a higher risk of hospital admission. The increased risk of hospital admission continued in the second and third year but was not statistically significant in the third year.

This information is important for counselling couples considering fertility treatment and adds further weight to the push for use of single embryo transfer (SET) in selected patient groups.

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

Funders of the project: NHMRC Grant #211930 (MH); NHMRC Program Grant #353514; NHMRC Fellowship #353628 (CB).

Pharmacovigilance in pregnancy using population-based linked datasets

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

Data linkage of population administrative data is being investigated as a tool

for pharmacovigilance in pregnancy in Australia. Records of prescriptions of known or suspected teratogens dispensed to pregnant women have been linked to a birth defects registry to determine if defects associated with medicine exposure can be detected. Records of births to the women who were dispensed PBS medicines in categories D or X of risk of medicine use in pregnancy were linked to the Western Australian Birth Defects Registry. There were 47 medicines in category D or X dispensed at least once during pregnancy with 23 associated with a registered birth defect to a woman dispensed the medicine. Most medicines showed an increased risk although not all were statistically significant, possibly due to the low volumes of dispenses. Medicines with the higher risks were medroxyprogesterone acetate (OR: 1.8; 95% CI: 1.4-2.3), follitropin alfa (OR: 2.5; 95% CI: 1.2-5.0), carbamazepine (OR: 3.1; 95% CI: 1.7-5.6), and enalapril maleate (OR: 8.1; 95% CI: 1.6-41.7). Many known associations between medicines and birth defects were identified, suggesting that linked administrative data could be an important means of pharmacovigilance in pregnancy in Australia.

Funders of the project: Australian Postgraduate Award to LC. NHMRC Program Grant #353514; NHMRC Fellowship #353628 (CB).

WA Register for Autism Spectrum Disorders

Emma Glasson, Sarah MacDermott, Glenys Dixon, Carol Bower.

The aim of the WA Register for Autism Spectrum Disorders is to monitor diagnostic trends of conditions characterized by autism (autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)). These disorders develop in young children and have significant life-long effects in the areas of social interaction, communication and behaviour. The WA Autism Register is ongoing and between 1999 and 2009 information has been collected on approximately 3,000 individuals.

During 2009, we gave a presentation about the WA Autism Register at the 2009 APAC (Asia Pacific Autism Conference) conference in Sydney. Representatives from the Register were approached to participate in an advisory capacity in the development of the proposed National Autism Register which is being progressed via FaCHSIA under the direction of Minister Bill Shorten. The Registrar, Dr Emma Glasson, was an elected member of the expert advisory panel for this project. Data from the WA Autism Register were published in the International Journal of Epidemiology regarding diagnostic trends of autistic disorders in WA, and this publication attracted media interest.

As well as existing for the purpose of local and national information, Register data are being used in an international collaboration making comparisons with an autism

register based in Denmark. This project was awarded funding from Autism Speaks (USA, value \$128,000) and the data are being prepared for publication.

Funders of the project: Funding and support for the WA Register for Autism Spectrum Disorders during 2009 included the Western Australian Department of Health, the Disability Services Commission of WA; and Autism Speaks (USA).

The influence of ambient air pollution from traffic emissions and pregnancy outcomes

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

Two papers were completed and published in peer-reviewed journals in 2009. One described a new method to geographically map health risks for case-control studies (Health and Place). The other looked at the risk of emergency department presentation for asthma using a variety of spatially defined exposure proxies, such as distance to roads and traffic density. Two peer-reviewed conference papers were published in proceedings. One was an investigation on the influence of confounding in relation to spatially variation in socio-economic position. The other described a new method to estimate background air pollution for environmental health studies. Finally, two papers are currently under review. The first is a review of the current evidence in relation to the effect of traffic-related air pollution on pregnancy outcomes. The other is a study

that assessed the association between background levels of ambient air pollution and the risk of emergency department presentation among children and young adults in Perth, WA.

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

Childhood Cancer

Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children

Elizabeth Milne, Carol Bower, Nick de Klerk, Ursula Kees, in collaboration with Bruce Armstrong, Frank van Bockxmeer, Michelle Haber, Murray Norris, Rodney Scott, Margaret Miller, Catherine Cole, Lin Fritschi, Judith Thompson, John Attia, Glenn Marshall, Liane Lockwood, Michael Rice, Luce dalla Pozza, Elizabeth Smibert, Frank Alvaro, Peter Downie.

Researchers in the Childhood Cancer Epidemiology program have been analysing the data collected between 2003 and 2007 in this national case-control study into the causes of childhood acute lymphoblastic leukaemia (ALL). The primary hypothesis of this study was that maternal folate supplementation during pregnancy protects against ALL in the offspring, with the effect modified by genetic factors in folate metabolism.

The following papers were published in

2009.

Maternal folate and other vitamin supplementation during pregnancy and risk of acute lymphoblastic leukemia (ALL) in the offspring

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

Fetal Growth and Risk of Childhood ALL: Results From an Australian Case-Control Study

We found that greater than expected fetal growth resulted in a higher risk of developing ALL in childhood. We think this is related to hormonal factors that are completely outside the mother's control and we plan to do more research on the reasons for higher rates of fetal growth.

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

- the mothers' diet during pregnancy;
- exposure to house painting
- exposure to pest control treatments in

the home or garden

- the types of jobs that parents had
- variations in genes that influence the way the body processes food and chemicals

Funders of the project: NHMRC Grant #254539.

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

Elizabeth Milne, Carol Bower, Nick de Klerk, Peter Dallas, in collaboration with Bruce Armstrong, Frank van Bockxmeer, Rodney Scott, John Attia, Lin Fritschi, David Ashley, Lesley Ashton, Judith Thompson, Murray Norris, Richard Cohn, Margaret Miller, Luce dalla Pozza, John Daubenton, Timothy Hassall, Maria Kirby, Stewart Kellie, Ross Pinkerton, Frank Alvaro, Angela Allesandri.

The Australian Study of Childhood Brain Tumours (AUS-CBT) is a national case-control study into the causes of childhood brain tumours (CBT). It aims to investigate genetic, dietary and environmental risk factors for CBT, and is the sister study to the Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (AUS-ALL). The study has been recruiting cases and controls since 2006; this will continue until the end of 2010.

The study involves children aged 0-14 years. Case children and their parents are recruited from the nine paediatric oncology units nationwide. Cases diagnosed in 2005 were recruited

retrospectively and the recruitment of cases diagnosed from 2006 onwards is ongoing. At the end of 2009, we had been notified of 527 eligible cases, of whom 431 (75.3%) were invited to participate and 290 (55.0%) consented. A total of 68 families have declined to participate and a further 56 were not invited due to medical and psychosocial reasons. Recruitment is ongoing and we are liaising with clinicians regarding further invitation and consent of the eligible families.

Control families are being recruited through national random digit dialing and are frequency matched to the case children by age, gender and State of residence. The control children have not been diagnosed with a CBT. AUS-CBT control family recruitment began in 2007 and six waves have been completed, with 640 families agreeing to participate when contacted by phone. Of these, 403 (63.0%) have given their consent.

The data collected include self-administered exposure questionnaires for both parents, food frequency questionnaires for both parents and the child, and telephone interviews regarding occupational and other exposures. In addition, we are collecting DNA samples from either blood or saliva for genotype analysis. Data collection for both the case and control families is progressing well. At the end of 2009, we had received exposure questionnaires from 611 families, food frequency questionnaires from 499 families and we had conducted 944 telephone interviews. DNA samples had

been provided by 511 families (including samples from the child and both parents), and 1184 samples had 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.

Funders of the project: NHMRC Grant #404089.

Nutrition and Genome Health in Children

Elizabeth Milne, Michael Fenech, Bruce Armstrong, Nick de Klerk, Margaret Miller.

The Nutrition and Genome Health in Children Study aims to identify key nutritional and genetic factors that may be associated with DNA damage in children. It looks to describe the nature of the interaction between nutritional and genetic factors in determining level of DNA damage in children, and also the associations between body mass index, DNA damage and micronutrient levels in children.

This study is a cross-sectional study of 450 Western Australian children, conducted between 2009 and 2011. Participants are children aged 3, 6 or 9 years at recruitment who have never been diagnosed with asthma, diabetes, cancer, arthritis or epilepsy. Participants and their

parents are recruited via primary schools, posters displays and flyers, advertisements in local newspapers and information letters distributed to a wide range of organizations. These include crèches, day care centres, playgroups, sports centres and libraries.

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

The study started in February 2009 and will continue until December 2011. The study is progressing well and is on track to complete participant recruitment by mid-2011. By the end of 2009, we had 180 parent consents, 165 participants had completed their telephone interviews, 161 had completed all blood collection, 157 had provided saliva samples and 136 had completed FFQs.

A preliminary analysis of micronutrient and DNA damage data collected from the first

100 children is almost complete. These results will inform the focus and timing of a proposed longitudinal extension to the study.

Funders of the project: NHMRC Grant#572623.

Collaboration for Applied Research and Evaluation

Infant Feeding in Western Australia: Establishing a Baseline and Evaluating the WA Department of Health's Baby Friendly Health Initiative Policy (BFHI)

Grant Smith, Tanyana Jackiewicz, Alicia Watkins.

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

The survey tool has been finalised and data collection will commence in March 2010. Preliminary results of the first survey will be available in October 2010.

Funders of the project: Western Australian Department of Health.

Gestational Diabetes in Western Australia

Grant Smith, Tanyana Jackiewicz, Rachel Skoss.

The aim of this project is to determine the outcomes associated with gestational diabetes and the cost of gestational diabetes to the health system in WA. The results of this research indicate that the rate of Gestational Diabetes (GDM) in Western Australia increased significantly from 1998 (34.3 per 1000 births) to 2007 (46.3 per thousand births). This translated to an increase each year of 1.3 per thousand births. If this trend was to continue to 2020 this would see the rate of GDM rise to 61.9 per thousand births; a 34% increase in the number of GDM cases. This potential rise in the incidence of GDM indicates a need for WA health system to assess future service provision requirements for the extra population of mothers receiving a GDM diagnosis. The relationship between GDM and a number of hospitalisation outcomes for mother and were examined. GDM strongly increased the odds of a child having a transitory metabolic/endocrine disorder, however most other outcomes were only weakly related to GDM or did not have a statistically significant association with the disorder. Whilst GDM was not strongly associated with the majority of negative outcomes examined as part of this research, it was found that the disorder was associated with a significant short-term cost to the health system. This cost was due primarily to the mother's

antenatal hospitalisations and the mother-related costs during the birth-event. The added cost to the health system associated with mother-related hospital costs in GDM pregnancies totalled approximately \$2.5 million in 2007.

However, whilst costs due to mother hospitalisations increased with a diagnosis of GDM, it was found that GDM was associated with large reduction in child hospitalisation costs in pregnancies that had mid-level or serious complications.

It is hypothesized that the protective effect of GDM for the child is not a result of any characteristic of the disorder itself, but rather occurred as a result of the extra services a mother receives after receiving a diagnosis of GDM (specifically the Diabetes Service located at KEMH). However, more research is required to conclusively determine that the blood-glucose levels associated with GDM does not have a protective effect on infant well-being through increased birth weight.

Funders of the project: Western Australian Department of Health.

Diabetes in Pregnancy: Factors affecting compliance with treatment and management regimes for Gestational Diabetes Mellitus (GDM)

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

This qualitative research aims to profile women's perceptions of GDM and their

views of the barriers and enablers to self-directed management of GDM. The information will assist in the development of strategies for clinicians to more effectively support women diagnosed with GDM to comply with recommended management approaches (principally diet, exercise and medication regimes). It is intended that the outcomes of the project will directly impact on service delivery to better meet the needs of women with GDM in all antenatal services. Project is expected to be completed by August 2010.

Funders of the project: Western Australian Department of Health.

Burns and Head Injuries Data Project

Grant Smith, Tanyana Jackiewicz.

This project aims to determine whether administrative data collected on contact with the health system could be used to target interventions toward children who are at greater risk of later experiencing a serious burn or TBI. This question was framed as a result of clinicians noting that the children presenting to hospital with a burn or TBI were likely to have had contact with the health system on prior occasions.

The two WA Department of Health data collections being used to explore this question are the Hospital Morbidity Database and the Emergency Department Database. Data is currently being analysed.

Funders of the project: Western Australian Department of Health.

Innovative Health Services for Homeless Young People Evaluation

Tanyana Jackiewicz, Tracy Reibel, Alicia Watkins.

In Australia, Innovative Health Services for Homeless Youth Program (IHSY) has developed a range of innovative service models that deliver health care to highly marginalised young people. IHSY services in Western Australia (WA) target young people at high risk aged between 12 and 25 years. This qualitative research project aims to construct a profile of the attributes of these services that enable them to work successfully with marginalised young people with complex needs, including Aboriginal young people; and report on recommendations for these and other community based services that can better meet the needs of this target group. We are in the process of interviewing and conducting focus groups with clients of five IHSY services in WA. We are asking them questions about their personal experiences, their perceptions and their suggestions as to the future of IHSY services and other community based services. We are also interviewing the deliverers of the services, who are partners in the research, to gain their perspectives on why they think their IHSY service is effective in reaching this target group and the future of services to young people. This research project has made a commitment to incorporating a philosophy of doing research with young people rather than to young people by ensuring that those involved in the study

are provided with some benefit for their involvement.

Funders of the project: Western Australian Department of Health.

Child and Adolescent Community Health (CACH) Evaluation Project

Tanyana Jackiewicz, Rachel Skoss.

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

TICHR has assisted CACH in providing critical reviews of the evidence relating to programs delivered by child and school health nurses for comprehensive home visiting, sleep and sexual health. TICHR has facilitated two workshops with service deliverers to discuss the evidence as well as facilitate a shared understanding of the role of child and school health nurses in these areas.

Funders of the project: Western Australian Department of Health.

ADHD Case Study Project

Roz Walker.

This project involves two stages, Stage 1: A comprehensive review of relevant national and international studies, policies and best practice which has informed the study objectives and identified future research areas. The literature includes studies of pathways to ADHD diagnosis, the barriers

and facilitators and their implications for this study. Stage 2 involves in depth interviews with parents of children with ADHD that meet the selection criteria. Interviews focused on their experiences along the pathway to a diagnosis of ADHD for their child/children, including their beliefs, knowledge and attitudes regarding ADHD; and the external barriers and facilitators that inform and influence their choices. The initial recruitment process to recruit families into the study was unsuccessful. A revised process was agreed upon by the DoH and ethics was resubmitted and approved. Clinicians, (paediatricians and child psychiatrists) across the metropolitan area in both public and private practices have agreed to participate in the study. Several eligible families have been identified and approached by clinicians. A case study methodology is being utilised. Key themes have been identified. Key findings to date include all parents in the study have tried alternative treatments to medication, many parents are profoundly impacted by the ongoing severity of their child's/ children's condition; several families have multiple children with ADHD, many of these children have other co-morbidities but the primary treatment is for ADHD, or the best outcomes for their child occurred after diagnosis and treatment for ADHD, many families feel complete isolation, alienation and stigma. Most expressed concern about their child expressing suicidal thoughts or attempting suicide. Several families had experienced separation or divorce which they

attributed to their partner not coping with their child/children's condition, had chosen to send their child/children to private school and secure private tuition to have additional academic and pastoral support, many were experiencing significant financial burden due to school and medical expenses for alternative treatments, special diets, and replacement of damaged household items.

Interviews will be completed by March 2010; the final report will be completed by April 2010 and will include:

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

Funders of the project: Western Australian Department of Health.

Developmental Pathways in WA Children Project

Fiona Stanley, Nick de Klerk, Jianghong Li, Anna Ferrante, Helen Leonard, Carol Bower, Merran Smith, Richard Mathews, Marilyn McKee, Leanne Barron, Andrew Marshall,

Vicki Caudwell, Ron Chalmers.

The Developmental Pathways in WA Children Project is a landmark project taking a multidisciplinary and holistic approach to investigate the pathways to health and wellbeing, education and juvenile delinquency outcomes among Western Australian children and youth. To achieve this, researchers from the Telethon Institute for Child Health Research and the University of Western Australia have been working in collaboration with a number of state government departments, including the WA Departments of Health, Education, Child Protection, Corrective Services, Communities, Indigenous Affairs, Treasury and Finance, Housing, Attorney General, Disability Services Commission, and WA Police. The project has established the process of linking together longitudinal, population-based data collected and stored by a large number of the WA government departments and the Telethon Institute, to create a fantastic cost-effective research and policy planning/evaluation resource. The project has also established a Directors' General Steering Committee who meet twice a year to discuss how to best use this joined up data and joined up agency resource.

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. Through the effective communication of the research findings, future government agency policies, practice

and planning initiatives will be more preventative, culturally appropriate and cost efficient, and we have encouraged cross-agency collaboration to ensure improved health, well-being and development of children and youth, their families and their communities.

Funders of the project: The Developmental Pathways in WA Children Project was made possible by the generous cash and in-kind contributions made by all of the collaborating organisations and government departments, which was matched by the Australian Research Council (ARC) through an ARC Linkage Project Grant.

Sub projects within the Project

The Developmental Pathways in WA Children Project supports several postgraduate students, to conduct individual research projects which answer specific research and policy relevant questions within and across the themes and scope of the overall project.

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

Eva Malacova

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). Key factors

include intrauterine growth; frequency, length and reason for hospital admissions; child mental and physical health status; and maternal characteristics, such as marital status. 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

Melissa O'Donnell

This project uses longitudinal population data from the Western Australian Government Departments of Child Protection, Health, Disability Services and Education which has been linked and de-identified through the Data Linkage Unit at the Department of Health. This administrative data has been used to investigate: hospital admissions related to child abuse and neglect to monitor trends over time and the injuries related to those admissions; the increased prior hospital morbidity for children who have contact with child protection services; the risk of child protection involvement for children born with Neonatal Withdrawal Syndrome; and the child and family characteristics of children with substantiated maltreatment.

Social and racial inequalities in

birth rates and infant outcomes in Western Australia

Amanda Langridge

This project uses longitudinal, administrative data from the WA Government Department of Health to examine trends in birth rates and investigate the effects of the Baby Bonus; investigate racial inequalities in poor fetal growth and preterm birth, and examine social inequalities in those outcomes by Aboriginality.

Do you see what I see? An exploration into the delivery of health, education and child protection services by the WA State Government to Aboriginal clients in the Perth Metropolitan and Geraldton Regions

Glenn Pearson

This qualitative research project explores how the delivery of health, education and child protection services provided by the WA State Government to Aboriginal clients is mediated by the perceptions Non Aboriginal and Aboriginal people hold of themselves and each other in the provision and receiving of these services.

On the dimensions and development of juvenile delinquency. A population-based study of the prevalence and frequency of offending and the influence of

individual, family and community factors on delinquency in Western Australian children

Anna Ferrante

The aim of this project is to contribute to a better understanding of the dimensions of juvenile delinquency and of the impact of various factors on the development of delinquency over the life-course. By exploring the interactions between risk factors and their effect on offending, it may be possible to map 'pathways' from early childhood to juvenile delinquency and later criminal behaviour.

Exploring the Pathways to Contact with Juvenile Justice in Aboriginal and Torres Strait Islander children: developing a profile of the risk and protective factors to support a strategy for change

Jocelyn Jones

This project seeks to develop a profile of the developmental, health, socio-economic, racial and demographic factors associated with risk, protective and resilience factors that contribute to juvenile delinquency in Aboriginal and Torres Strait Islander Children.

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

Kristine Northey

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

Desiree Silva

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.

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.

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

Anke van Eekelen, Eugen Mattes, 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 2009, we finalized the collection of (i) data in the field of mental health and cognitive and neuroendocrine

development as part of the Raine Study follow up at 17 years of age. We have made progress in the collection of data on stress responsiveness at the Raine Study stress test at 18 years of age with the completion of 950 stress tests at the end of 2009. Analysis and manuscript preparation for publication of the 17 year outcomes on stress adaptiveness in the Raine cohort has started in 2009.

Funders of the project: 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.

Intellectual Disability

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

Jenny Downs, Ami Bebbington, Philippa Carter, Peter Jacoby, Anne-Marie Williams, Kitty Foley, Simon Williams, Soumya Ghosh, Walter Kaufmann, Helen Leonard.

Since Rett syndrome is a movement disorder, an extremely important and innovative source of study data is video footage provided by the subjects' families. Many families participating in the Australian Rett Syndrome Database have recorded video footage showing their daughters' participation in activities of daily living,

and have provided video footage in 2004 and more recently in 2007/2008. This is an ongoing study.

We have developed validated coding systems for gross motor function, hand function and hand stereotypes. As cross-sectional studies, data from unique cases have been analysed in relationship to age and genotype, giving a greater understanding of the phenotype of Rett syndrome. Further, we have preliminary evidence to support the validity of the measures that we 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.

Over 200 families have provided a video of their daughter and seventy on two occasions. We have coded function at two time points approximately 3 ½ years apart to describe the stability of these skills for these subjects. Data analysis for this longitudinal component is currently being undertaken. The collection of additional videos is being planned to increase the power of this analysis.

Funders of the project: NHMRC Program Grant#353514; NHMRC Grant#303189.

International: InterRett

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

The InterRett project is now in its 8th year and continues to thrive with a renewal of

funding for 2010 and an increase of over 20% in case submissions during 2009. This dataset, the largest of its kind in the world, provides statistical power for meaningful research and the ability to compare sub-groups within the cohort. Analysis of these data is now a major focus, together with ongoing case ascertainment and international collaboration. Findings from five studies that utilized the InterRett data were published in peer-review journals in 2009. A further six are underway, three of which involve collaborations with interstate and overseas colleagues. During 2009, a Chinese colleague joined our study for one month to carry out a study of epilepsy in Rett syndrome and a follow-up visit to Beijing was planned for further collaborative work. The family questionnaire, previously offered in five languages, was recently made available online in Dutch and a Polish version is under development. By breaking down the language barrier the InterRett project provides opportunity for overseas family associations to make an important contribution to Rett syndrome research.

Funders of the project: International Rett Syndrome Foundation.

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

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

Gordon Baikie, Sue Fyfe, Anne McKenzie, Carolyn Ellaway, Ian Torode.

Scoliosis develops in approximately 75% of girls with Rett syndrome by 13 years of age. Despite this, there is limited literature of management strategies for scoliosis in Rett syndrome that can support clinical management. Because of the rarity of Rett syndrome, clinicians typically see small numbers of patients and it is difficult to develop significant clinical expertise.

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

Since publication, we have been implementing a plan for the dissemination of these results to both clinicians and families. In the first instance, we produced the guidelines into more readily digestible formats. We produced a booklet that described the guidelines supplemented with relevant pictures and direct quotes from families illustrating their experiences. We also summarized the guidelines contained in the journal article in the format of a leaflet and this is inserted inside a booklet as a handy reference.

Distribution of the booklets to relevant stakeholders has commenced and will be an ongoing process. Hard copies of the booklet have been distributed by mail to families in Australia, in the UK via the Rett Syndrome Association UK, and in the US via the International Rett Syndrome Foundation. They have already been distributed to clinicians participating in the project and to Rett syndrome clinics in the US and more widespread distribution to clinicians will commence shortly. The booklet and leaflet have also been made available on relevant websites and the booklet is currently being translated into Polish.

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

Developing clinical guidelines for the management of gastro-intestinal disorders in patients with Rett syndrome

Jenny Downs, Helen Leonard, Gordon Baikie, Madhur Ravikumara, Nusrat Nasseem

Rett syndrome is often associated with poor growth, in part from feeding difficulties and/or gastro-oesophageal reflux. Co-morbidities such as constipation and abdominal bloating are also common. Similar to our findings in the scoliosis management study, there is limited literature of management strategies for these common gastro-intestinal disorders in Rett syndrome and we currently using the Delphi technique to collate the views

of clinicians and develop a consensus on management.

This project is in progress. Our methods have thus far included assessment of the perspectives of parents on these issues and systematic review of the literature. We are currently amalgamating information collected from both of these sources to form a document for circulation in the first phase of the Delphi process. We are also recruiting an expert panel which is both international and multi-disciplinary in nature who will participate in the Delphi process and provide feedback on the first and subsequent drafts until a consensus is reached.

Funders of the project: Rett Syndrome Association UK.

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

Helen Leonard, Carol Bower, Nick de Klerk, Sue Fyfe, David Ravine, John Christodoulou, Carolyn Ellaway, Lakshmi Nagarajan, Sheena Reilly, Helen Woodhead, Jenny Downs, 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 and Professor Alan Percy from the University of Alabama.

Progress continues with analytical investigations using data relating to different aspects of the study and during 2009 eight articles relating to the study were published or accepted for publication. These included assessing the impact of polymorphisms in the BDNF gene on

clinical severity, an evaluation of the impact of scoliosis surgery on activities of daily living, the variation of hand stereotypies in Rett syndrome, the profile of cases with C terminal deletions, the relationship between the use of valproate and the risk of fractures, pain insensitivity in Rett syndrome and the variation in hand function and its determinants. Other work undertaken during 2009 involved comparing recent survival in Rett syndrome with that of the series of Austrian cases originally described by Professor Andreas Rett.

Funders of the project: NHMRC Program Grant#353514 US National Institutes of Health.

CDKL5

Helen Leonard, John Christodoulou, Meredith Wilson, Alison Anderson, 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.

Funders of the project: International Rett Syndrome Foundation.

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

Helen Leonard, Alison Anderson, Sue Fyfe, John Christodoulou, David Ravine, Jenny Downs.

The final chapter of this project involved a recent visit to Beijing by three of our research team to consolidate current collaborate work and establish clear directions for future investigations. Future plans agreed to included the submission of two grant proposals to the International Rett Syndrome Foundation to carry out 1) a genotypic phenotypic Australian China study with laboratory work being done in China and 2) to support the development of a Rett syndrome family association in China. Ongoing are: an investigation into the process and impact of Rett syndrome diagnosis in China which complements a recent study on the same topic based on the Australian and International Rett syndrome cohorts; an investigation into the feasibility of collecting video material on children with Rett syndrome in China; and completion of a manuscript on epilepsy arising from analysis of clinical data undertaken by our colleague Dr Bao during a month long stay at the Institute in 2009. Dr Bao's visit was funded by an

AusAID fellowship awarded as a result of our recent collaborations. Overall the travel funding received under Australian-China award has allowed us to strengthen our relationship with China and forge exciting new opportunities.

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

IDEA - Intellectual disability exploring answers

Carol Bower, Helen Leonard, Jenny Bourke.

IDEA Advisory Council 2009: Professor Carol Bower, Dr Helen Leonard, Jenny Bourke, (TICHR), Dr Simon Williams (PMH), Dr Vera Morgan (UWA), Richard Sanders (Autism Association of WA), 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 (DSC) since 1953, as well as information from the Department of Education for births since 1983. IDEA is currently updated with notifications of children identified with an intellectual disability from the Department of Education and Training and the Disability Services Commission to the end of 2006. These records are linked by the Western

Australian Data Linkage Unit (DLU) to each other and to all current notifications on the database, in order to minimise any duplications. In 2009 an application for linkage of DSC and Education records to the end of 2008 was lodged with the DLU and is pending.

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 2009 were: Exploring the Pathways to Contact with Juvenile Justice: developing a profile of the risk and protective factors to support a strategy for change; and

Alcohol in pregnancy: Health outcomes and use of hospital services by women with a recorded alcohol-related condition during pregnancy and their offspring.

Funders of the project: Disability Services Commission.

The transition from secondary school to adulthood: Experiences and life outcomes for youth with an intellectual disability and their families

Helen Leonard, Carol Bower, Nick de Klerk, Gwynnyth Llewellyn, Stewart Einfeld, Trevor Parmenter, Vivienne Riches, Bruce Tonge, Nick Lennox, Ron Chalmers, John Brigg, Greg Lewis, Jackie Softly, Jenny Bourke, Paula Dyke, Glenys Dixon.

This project, which developed from an ARACY Seed-funding grant, seeks to explore the challenges faced and outcomes achieved by students with an intellectual disability (ID) as they move from secondary school into adult life. The study will investigate the factors at an individual, educational, family, and societal level which positively and adversely affect outcomes for young people with an intellectual disability and their family. The aim is to determine the experiences of young people with an ID moving from school to adult life and, in the process, determine what is a 'good' outcome from all perspectives. There are likely to be major life changes for young people with ID as they move into adulthood with respect to work, where they live, who cares for them, how their health and therapy needs are managed and how they will spend their days.

In 2009, qualitative interviews were conducted with 15 families of children with Down syndrome and 15 with Rett syndrome. A number of key themes emerged from rich qualitative data that described the 'lived' transition experiences for families and young people with an ID. These primarily related to information and support from service providers; family impact emotionally and financially; and quality of life changes for both families and the individual with ID. These interviews were used to inform the development of questionnaires based around transition using the International Classification of Functioning (ICF) as a framework. Families in WA with a young person

with Down syndrome, as well as families across Australia with a daughter with Rett syndrome have been forwarded the questionnaire.

Funders of the project: Australian Research Council.

WA Cerebral Palsy Studies

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

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

The Western Australian Cerebral Palsy Register

Linda Watson, Eve Blair, Fiona Stanley.

The WA CP Register, now in existence for 30 years, is used to monitor the occurrence of CP in WA, carry out research to investigate its causes and evaluate treatment strategies, identify CP as a long-term outcome in other WA studies and assist in the planning of services for people with CP. A birth cohort is included in analyses after case data are updated at age 5 years; the Register is now considered complete to 2004.

The WA Register is now also responsible for contributing data to the Australian CP Register (ACPR), a national collaboration initiated by the WA team which was established to provide information about CP throughout Australia as well as a larger study population to enable more effective research. The administrative centre has now moved to the Cerebral Palsy Institute in NSW where it continues to flourish. See graph below.

Developing a reliable system of classifying CP

Sarah Love, Noula Gibson, Eve Blair, Linda Watson.

The cerebral palsies include a wide range of motor impairments across the spectrum of severities, and research therefore depends on consistency in classifying CP subgroups. International attention has been focused on the challenge of standardising the recording of motor impairments for several decades, and WA has long been at the forefront in developing a reliable system of describing the clinical features of CP. We are currently trialling an innovative diagrammatic limb-by-limb CP Description Form which incorporates the Australian Spasticity Assessment Scale (ASAS) devised by Sarah Love and Noula

Gibson, who have led this work. A Training and Reference video demonstrating the use of the ASAS as well as the features of different forms of CP is also in preparation.

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

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

Comprehensive maternal, birth and neonatal information on CP cases, matched controls, and a sample of unexplained perinatal deaths born 1980-1995 was collected from birth hospitals throughout the State providing a wealth of data enabling causal pathways to the different outcomes to be compared. The primary aim of these studies is to prevent the occurrence of brain damage responsible for CP by identifying points on each causal pathway to CP at which it may most effectively, efficiently and ethically be interrupted. Data analysis continues with the intent to explore causal pathways and report research findings at international forums.

Kate Taylor investigated the topic of vanishing twins and CP, quantifying the contribution to CP of co-fetal deaths at or after 20 weeks gestation and co-fetal losses before 20 weeks gestation. This work is now published. Eve Blair has examined the association between pre-eclampsia and CP which is soon to be published, and Jan de Groot is looking at trends in CP following admission to neonatal intensive care. Jan's work was

presented at the 3rd International CP Conference in Sydney where she won the Cerebral Palsy Foundation Promising Researcher Award and again at the 20th European Society of Pediatric and Neonatal Intensive Care (ESPNIC), in Verona, Italy, June, 2009. Sarah McIntyre is studying antecedent factors in term CP cases and presented her preliminary findings at the 3rd International CP Conference, Feb 2009.

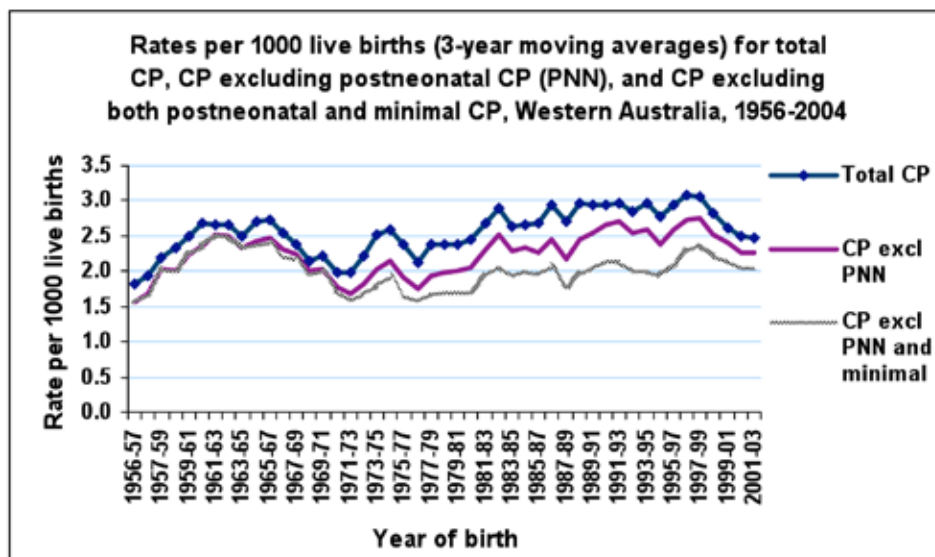
Funders of the project: The WA Cerebral Palsy Register and Case-control Studies were funded by NHMRC Program Grant #353514 (2005-2009). PLAN Australia has generously funded the development of the ASAS, the CP Description Form and the Training and Reference DVD. A PMH Foundation Special Project Grant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

Infectious Diseases

Aetiology, burden and causal pathways of acute lower respiratory infections using population linked data

Hannah Moore, Deborah Lehmann, Peter Jacoby, Nick de Klerk, Heather D'Antoine, Daniel McAullay in collaboration with Peter Richmond, David Smith, Tony Keil.

Acute lower respiratory infections (ALRI),



or chest infections like influenza and pneumonia, are a major cause of illness in young children. The primary objective of this project is to describe the aetiology, burden and causal pathways of ALRI in Aboriginal and non-Aboriginal children from a 10-year birth cohort (245, 249 births) using population linked data from the Western Australian Data Linkage System. Data cleaning and analysis of the hospital morbidity database was the focus for 2009. We identified 26,106 hospital episodes for ALRI between 1996 and 2005. These episodes have been further classified into separate ALRI diagnoses: whooping cough, pneumonia, bronchiolitis, influenza, other ALRI and bronchitis. Just under one third (n=7864, 30.1%) of these ALRI episodes are in Aboriginal children, highlighting the disproportionate burden of ALRI in Aboriginal children compared to non-Aboriginal children. Among children born 1996-2005, 6.5% of all non-Aboriginal children and 25.6% of all Aboriginal children were admitted at least once for an ALRI during the same time period. Analyses of these data in 2009 include:

- Seasonality of bronchiolitis and RSV-related hospitalisations varies between health regions of WA. As a result, different RSV immunoprophylaxis schedules are needed, especially for the northern tropical regions where seasonal duration of bronchiolitis and RSV-related illness is consistently longer than in temperate areas of WA.
- Pneumonia hospitalisations declined in all children, particularly in Aboriginal

children. Between 1996-2000 and 2001-2005 all-cause pneumonia hospitalisation rates fell by 28-44% in Aboriginal children aged 6-35 months. Hospitalisations for pneumococcal pneumonia have declined by 37%/annum in Aboriginal children aged 6-11 months.

- Disparity in pneumonia hospitalisations between Aboriginal and non-Aboriginal children aged 6-11 months has declined from being 15 times higher in Aboriginal children compared to non-Aboriginal children in 1996-2000 to 10 times higher in 2001-2005.
- Factors leading to increased risk of ALRI for both Aboriginal and non-Aboriginal children are: being born in autumn, high parity, male gender and maternal smoking during pregnancy. In Aboriginal children, being born to a teenage mother and poor socio-economic status have been identified as major risk factors. In non-Aboriginal children, elective caesareans have been identified as an important risk factor for ALRI.

These findings have been presented at the 6th World Congress for the World Society for Paediatric Infectious Diseases and various local meetings. One letter to the editor has been published and another manuscript is under review. The work documenting the decline in pneumonia hospitalisations has been selected for an oral presentation in the 7th International Symposium on Pneumococci and Pneumococcal Diseases in early 2010. Cleaning and coding commenced for the Emergency Department Data Collection

of 19,807 metropolitan emergency department presentations for ALRI between 2001 and 2005. Negotiations with data custodians of laboratory data continued in 2009 and data have been received in early 2010.

Funders of the project: NHMRC Project Grant #572590.

Preventing Otitis Media to Give a Sound Start for School

Deborah Lehmann, Ruth Monck, Wendy Sun, Margaret Wallam, Daniel McAullay, Tanyana Jackiewicz in collaboration with Anne Mahony, Charles Douglas, Bega Garnbirringu, Francis Lannigan, Sharon Weeks, Christine Jeffries-Stokes.

This 3-year project follows on from findings of the Kalgoorlie Otitis Media Research Project. We reported very high rates of otitis media (OM) and associated hearing loss, high carriage of bacteria in the upper respiratory tract (which predisposes to OM) from a very young age in Aboriginal children and an increased risk of OM among children exposed to environmental tobacco smoke. The overall aim is to have Aboriginal children hearing well by the time they start school.

The objectives of this project are to:

- (1) Develop and implement a multifaceted ear health promotion program in collaboration with Aboriginal organisations in the Goldfields.
- (2) Evaluate the impact and effectiveness

of an ear health promotion program that includes (a) an awareness program, (b) training of Community Health Nurses and Aboriginal Health Workers in screening and health promotion and (c) a screening program for OM.

- (3) Evaluate use at primary health care level of a simple tool (which measures otoacoustic emissions) that can detect fluid in the middle ear at a very young age and hence identify a target group of children at subsequent risk of developing OM.
- (4) Evaluate the overall program in terms of feasibility and sustainability.

Fourteen Aboriginal Health Workers and 7 Community Health Nurses attended a workshop on ear health in August 2009. We received very positive feedback but also a strong request for further training. We have developed a flow chart for management of OM in Aboriginal children which is also being distributed to medical practitioners in the region. Ear screening has begun in Kalgoorlie, Laverton, Leonora and Coolgardie. All these places have tympanometers. Each location is working on ways of incorporating the ear screening into their daily clinics. We have visited communities 4 times and plan to visit every 2 months to provide support. In 6 months 61 Aboriginal children age < 5 years from Laverton, Leonora, Coolgardie and Kalgoorlie have been enrolled into the project and had their ears checked. There has been a large increase in referrals to Dr Lannigan's clinic at Bega Garnbirringu Aboriginal Medical Service.

In order to evaluate the impact of the awareness and health promotion program we have interviewed with community members to assess knowledge and practice around ear disease, smoking, hygiene practices prior to such a program. This will be repeated in 2-3 years' time. The video-otoscope, which allows people to see the ear drums on a laptop screen, is an excellent educational tool. We have used it at each site visit and during NAIDOC week. A local artist prepared a banner promoting good ear health which was carried by study team members in the NAIDOC week parade in Kalgoorlie. A community arts project around OM and its prevention, including song writing will be developed in 2010.

The study was presented at the Goldfields Ear Health Conference.

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

Hospitalisation for diarrhoea among Western Australian children

Karthik Raj Manoharan, 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 investigates the trends in hospital admissions for diarrhoeal diseases (gastroenteritis) in Western Australian children aged <15 years between 1983 and 2006.

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

Funders of the project: NHMRC Program Grant #353514.

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

Deborah Lehmann, Hannah Moore, Joel Tan in collaboration with Carolien Giele, Michael Watson, Tony Keil, Peter Richmond, Helen Smith.

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 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 worldwide annually. IPD primarily

affects the very young and the elderly. In 2001 Australia introduced a unique 7-valent pneumococcal conjugate vaccine (7vPCV) 2-4-6 month schedule with a 23-valent pneumococcal polysaccharide vaccine (23vPPV) booster for Aboriginal children aged 18 months. In 2005, 7vPCV was made available for all Australian children. We investigated the impact of the vaccination programs on the population trends of IPD. Following introduction of 7vPCV, IPD rates in Aboriginal children have declined by 46% in those aged <2 years and by 40% in those aged 2-4 years. The IPD rate in non-Aboriginal children has fallen by 64% in children aged <2 years since the introduction of 7vPCV and by 51% in those aged 2-4 years. We have seen a herd immunity effect with a decline in IPD rates in non-Aboriginal adults aged 50 years and over. However, of concern is the dramatic increase in rates of IPD in young Aboriginal adults aged 30-49 years from 59 per 100,000 population/year to 110/100,000. As a result the rate of IPD in Aboriginal people compared to non-Aboriginal people has increased from being 6 times higher in 1997-2001 to 12 times higher in 2005-2007. This increase is predominantly due to an increase in non-7vPCV serotypes. The emergence of serotype 19A as an important cause of IPD in the non-Aboriginal population has been published in the Medical Journal of Australia. A manuscript documenting trends in Aboriginal and non-Aboriginal people in WA has recently been accepted for publication in an international journal.

Funders of the project: Western Australian

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, Joel Tan, in collaboration with Jacinta Bowman, Jade Jones, Tom Riley, Carolien Giele, Paul Effler, Amanda Leach, Kim Hare, Heidi Smith, Peter Richmond.

Streptococcus pneumoniae (*pneumococcus*) can cause middle ear infections and invasive pneumococcal disease (IPD) resulting in meningitis, pneumonia and septicaemia (blood poisoning). The Australian Aboriginal population has among the highest reported IPD rates worldwide. The existence of 92 knowntypes (serotypes) of pneumococci increases the challenge of prevention. A pneumococcal conjugate vaccine (Prevenar™) covering the 7 most common serotypes causing IPD in industrialised countries and a booster with a pneumococcal polysaccharide vaccine (Pneumovax™) covering 23 serotypes has been offered to Aboriginal children since 2001 and Pneumovax is also offered adults. While there has been a marked reduction in IPD due to vaccine serotypes, there has been an increase in rates of IPD due to serotypes not included in the Prevenar vaccine, particularly a marked increase in young Aboriginal adults.

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 pernasal swabs from Aboriginal adults and 300 from Aboriginal children in metropolitan, urban, rural and remote areas of Western Australia annually. We also collect ear swabs from children with middle ear discharge. Other study aims include: i) describing the prevalence of upper respiratory tract (URT) carriage of other pathogens identified on primary culture; ii) comparing pneumococcal carriage rates in Aboriginal children aged < 2 years in the Kalgoorlie-Boulder region with those documented in 1999-2005; iii) comparing the distribution of pneumococcal serotypes in the URT with those causing IPD in Aboriginal adults and children annually; iv) storing pernasal swabs for detection of viruses by PCR to describe the prevalence of respiratory viruses; and v) investigating viral-bacterial interactions in the URT.

We recruit study participants attending health services for routine examination, immunisation or illness and also through home-visiting. To date we have collected 654 pernasal swabs and 29 swabs of discharge from the middle ear from a

total of 150 children aged < 5 years and 334 older children and adults who were living in Wiluna, Kalgoorlie, Roebourne, Kununurra, Broome, Beagle Bay or Geraldton or else attending one of four Aboriginal Medical Services in the Perth metropolitan area. Pneumococci were grown from 71% of pernasal swabs collected from children and 31% from those aged ≥ 5 years. Haemophilus influenzae grew in 66% of swabs from children aged <5 years and 22% from swabs from older people, while equivalent figures for Moraxella catarrhalis were 69% and 24%, respectively. 36 different serotypes have been identified and an unknown serotype belonging to serogroup 6 has been isolated and is currently being investigated further. Prevnar has successfully eliminated carriage of serotypes included in this vaccine since only 10% of pneumococci were Prevnar serotypes. In contrast 56% of pneumococci in the URT were serotypes that are not covered by either Prevnar or the 10-valent and 13-valent pneumococcal conjugate vaccines that have recently been licensed. The study is ongoing. Our findings to date have been presented at the Goldfields Ear Health Conference and will be presented at the 7th International Symposium on Pneumococci and Pneumococcal Diseases in Tel Aviv in early 2010.

Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation and NHMRC Project Grant #545232 (a collaboration with Menzies

School of Health Research).

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

Deborah Lehmann, Peter Jacoby, Wenxing Sun, Christine Jeffries- Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane, Ruth Monck, Fiona Stanley, in collaboration with Bega Garbiringu Health Services Aboriginal Corporation, Ngunyitju Tjitji Pirni Inc, Harvey Coates, Thomas Riley, Sharon Weeks, Allan Cripps, Jennelle Kyd, Jacinta Bowman, Amanda Taylor, David Smith, Denise Murphy, Amanda Leach, Nevada Pingault.

Otitis media (OM, middle ear infection) can seriously affect childhood development, school performance and subsequent social and economic well-being. The Kalgoorlie Otitis Media Research Project was established in 1999 to investigate the causal pathways to OM and, specifically, to identify demographic, socio-economic, environmental, microbiological and immunological risk factors for OM in Aboriginal and non-Aboriginal children in order to develop appropriate interventions. We followed 100 Aboriginal and 180 non-Aboriginal children from birth to age two years. Field work was completed in 2004 and data cleaning was completed in April 2005.

The peak prevalence of OM in the Kalgoorlie-Boulder area was 72% in

Aboriginal children aged 5-9 months and 40% in non-Aboriginal children aged 10-14 months. Almost one-third of Aboriginal children and 5% of non-Aboriginal children had a perforated ear drum at least once by age 2 years, and 65% of Aboriginal children and 23% of non-Aboriginal children have some degree of hearing loss at age 12-17 months.

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 found that rhinoviruses were associated with carriage of Haemophilus influenzae and Moraxella catarrhalis in Aboriginal children. Adenoviruses were positively associated with carriage of H. influenzae in Aboriginal children and M. catarrhalis in non-Aboriginal children, but negatively associated with Streptococcus pneumoniae in Aboriginal children. These findings have been reported in a manuscript accepted for publication in an international journal.

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

We have investigated antimicrobial susceptibility of *M. catarrhalis* strains isolated from children in this study. A large proportion of strains were resistant to ampicillin and/or co-trimoxazole. Therefore, current therapeutic guidelines, which recommend amoxicillin for treatment of otitis media, may need to be revised. These findings are in press in an international journal. We have also documented for the first time simultaneous carriage of multiple strains of *M. catarrhalis*.

Finally, we found that crowding is associated with increased risk of carrying the OM-associated pathogens *S. pneumoniae*, nontypeable *H. influenzae* or *M. catarrhalis* in the URT, but living in a larger house attenuated this effect in Aboriginal children. Daycare attendance predicts carriage of the same OM-associated pathogens in non-Aboriginal children while exclusive breastfeeding for the first 6-8 weeks of life protects children from carriage of *Staphylococcus aureus*.

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

Infectious Diseases Community Reference Group

Deborah Lehmann, Hannah Moore, Kirsten Alpers, Anke Bergmann, Wendy Sun, Anne McKenzie.

In 2007 we convened an Infectious

Diseases Community Reference Group to inform the wider community about research conducted at ICHR around infectious diseases and for community members to provide researchers with their valuable input into research projects. This group consists of 13 members including 8 community members (of which 3 are Aboriginal), 2 researchers, 1 representative from the Western Australian Department of Health, 1 representative from the Kulunga Research Network and 1 representative from the Institute for Child Health Research Consumer and Community Advisory Council. This group met four times in 2009 and discussed the progress of the research projects associated with infectious diseases at ICHR.

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

Neonatal immunisation with pneumococcal conjugate vaccine in Papua New Guinea

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

Throughout the world an estimated 820,000 children die annually from pneumococcal disease, the majority in early infancy. This study 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 (7vPCV) on early pneumococcal nasopharyngeal colonisation and on the incidence of acute respiratory infections in the first year of life. We are investigating the development of mucosal and T-cell immunity to non-capsular pneumococcal protein antigens and how this may be affected by early onset of colonisation. The study is also assessing the impact of neonatal immunisation on humoral and cellular immune responses to concomitant vaccines (diphtheria toxoid, tetanus toxoid and measles) and whether PCV interferes with normal maturation of the immune system.

A total of 318 children were enrolled; 80% completed follow-up at 18 months of age. 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. Results to date show no deleterious effect of neonatal 7-valent PCV (7vPCV). 7vPCV is immunogenic in PNG neonates and young infants, and in a neonatal or early infant schedule primes for immunologic memory for 7vPCV serotypes with booster response to pneumococcal polysaccharide vaccine (PPV) at age 9 months and sustained serotype-specific antibody concentrations to age 18 months. PPV also induces good antibody responses for some pneumococcal serotypes that are

not included in PCVs but commonly cause disease. 70% of neonates were colonised with *Streptococcus pneumoniae* by age 1 month. 51 different pneumococcal serotypes have been identified in the upper respiratory tract. At age 9 months, 68-78% of pneumococci were non-7vPCV serotypes. Analysis of cellular immune responses 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

Ms Jacinta Francis from the Papua New Guinea Institute of Medical Research was awarded a Masters Degree 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.

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.

A 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 “as prevalent as” when children were healthy.

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

Nutrition

Cardiometabolic (obesity, cardiovascular disease, type 2 diabetes, liver injury) and mental health disorders are of increasing population health concern for Australia as well as globally. The primary aim of the nutrition team is to describe relationships between nutritional factors, cardiometabolic and mental health disorders from infancy to adulthood. We are using data collected in the Western Australian Pregnancy Cohort (Raine) Study which commenced in 1989 and is one of few pregnancy cohorts in the world. A wide range of data have been collected during pregnancy, at birth (n=2868), and at 1, 2, 3, 6, 8, 10, 14 and 17 years. The 21 year follow-up will be complete by early 2012. Existing and newly collected data is being used for this project and

replication of findings are being reported in collaboration with the large UK Avon Longitudinal Study of Parents and Children (ALSPAC) study. The Raine study is ideally placed for a life course approach in cardiometabolic and mental health disorders. By examining these trajectories to 21 years we are identifying early determinants of risk and key times for intervention.

In 2009 the Nutrition team were involved in a range of topics listed below.

Dietary Patterns and Adolescent Mental Health

Wendy Oddy, Monique Robinson, Gina Ambrosini, Therese O’Sullivan, Nick de Klerk, Lawrence Beilin, Sven Silburn, Stephen Zubrick, Fiona Stanley.

Our objective in this study is to investigate associations between dietary patterns and mental health in early adolescence. The Western Australian Pregnancy Cohort (Raine) Study is a prospective study of 2,900 pregnancies recruited from 1989-1992. At 14 years of age (2003-2006; n=1,324), the Child Behaviour Checklist (CBCL) was used to assess behaviour (characterising mental health status), with higher scores representing poorer behaviour. Two dietary patterns (Western and Healthy) were identified using factor analysis and food group intakes estimated by a 212-item food frequency questionnaire. Relationships between dietary patterns, food group intakes and behaviour were examined using general

linear modelling following adjustment for potential confounding factors at age 14: total energy intake, body mass index, physical activity, screen use, family structure, income and functioning, gender and maternal education at pregnancy. We showed that higher total (b=2.20, 95%CI= 1.06, 3.35), internalizing (withdrawn/ depressed) (b=1.25, 95%CI= 0.15, 2.35) and externalizing (delinquent/aggressive) (b=2.60, 95%CI= 1.51, 3.68) CBCL scores were significantly associated with the Western dietary pattern, with increased intakes of takeaway foods, confectionary and red meat. Improved behavioural scores were significantly associated with higher intakes of leafy green vegetables and fresh fruit (components of the Healthy pattern). We concluded that our findings implicate a Western dietary pattern in poorer behavioural outcomes for adolescents. Better behavioural outcomes were associated with a higher intake of fresh fruit and leafy green vegetables.

Funders of the project: Raine Medical Research Foundation, NHMRC Program Grant#353514, Telstra Research Foundation, Australian Rotary Health Research Fund, Western Australian Health Promotion Foundation (Healthway).

Essential fatty acids and adolescent mental health

The Nutrition team has also been involved in a project studying the essential fatty acids in the diet and their effects on child mental health.

Intake of essential fatty acids is associated with a decreased risk of depression in adolescents.

Wendy Oddy, Michael Smith, Nicholas de Klerk, Trevor Mori, Lawrie Beilin, Gina Ambrosini, Monique Robinson, Therese O’Sullivan, Sven Silburn.

Background: Omega-3 polyunsaturated fatty acids (n-3 PUFA) may be beneficial in reducing symptoms of depression. However there is limited evidence regarding the influence of dietary n-3 PUFA intake on mood in adolescents from population studies. In the present investigation, we aimed to address the question of the relationship between dietary and n-3 PUFA intake on depression symptomatology in a large prospective pregnancy cohort. The procedure for this study entailed using adolescents enrolled in the Western Australian Pregnancy Cohort (Raine) Study who completed a Food Frequency Questionnaire (FFQ) to assess dietary fatty acid intake, as well as other dietary factors at 14 years (y). A fasting blood sample was collected for biochemical analyses to validate dietary intake. Participants also completed the Beck Depression Inventory for Youth (BDI-Y) at 14y (N=1,407) and 17y (N=995). Cross-sectional and longitudinal analyses were conducted using Spearman’s correlations and linear regression in models unadjusted and adjusted for other dietary and metabolic factors. Our results showed that the FFQ and BDI-Y were completed by 1,407 adolescents at 14 y. In addition, 995 participants completed

the FFQ at 14y and the BDI-Y at 17y. FFQ and erythrocyte values were significantly correlated for EPA, DHA, n-3 PUFA and total n-3 PUFA. Significant inverse relationships were observed between both n-3 and n-6 fatty acid intake at 14y and BDI-Y scores at both 14y and 17y. These associations were considerably attenuated however, following adjustment for other dietary and metabolic confounders. From this study we concluded that there may be potential short- and long-term benefits of essential fatty acid intake particularly n-3 PUFA in reducing depressive symptoms in adolescents. Much of this relationship may be accounted for by other dietary factors however, including overall intakes of energy, fat and cholesterol, and metabolic factors.

Funders of the project: Nationally competitive Heart Foundation/ Beyond Blue Strategic Research Initiative grant.

Attention-Deficit/Hyperactivity Disorder (ADHD) and dietary patterns.

Amber Howard, Monique Robinson, Grant Smith, Jan Piek, Wendy Oddy.

The Nutrition team was involved in a project with a Masters of Clinical Psychology student, Ms Amber Howard.

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterised by a persistent pattern of inattention and/or hyperactivity. The aetiology of ADHD is unknown however diet has been implicated as one contributing factor. This current study's

aim was to investigate the association between ADHD diagnosis and adolescent dietary patterns. Nutritional data were collected from 1,631 Food Frequency Questionnaires (FFQ) completed in the 14-year follow-up of the Western Australian Pregnancy Cohort (Raine) Study. 'Healthy' and 'Western' dietary patterns were identified with factor analysis. ADHD diagnoses were identified via parental reports. Control variables included pregnancy and lifestyle factors known to influence mental health. ADHD diagnosis and dietary pattern associations were determined using step-wise multinomial logistic regression. We found that 'Western' dietary patterns were significantly associated with ADHD diagnosis and despite a lack of significance, results were in the expected direction with 'Western' dietary patterns increasing the risk for 'Inattentive' AD/HD over 'Combined' ADHD. 'Healthy' dietary patterns were not significant with any measure. Four other factors also had significant associations with ADHD diagnosis. As expected, gender was a significant risk with more boys diagnosed with ADHD. Increased maternal stress during pregnancy seemingly increased the risk for 'Combined' ADHD, whereas increased maternal age at conception appeared to decrease the risk for 'Inattentive' ADHD. Also, increased levels of physical activity appeared protective against the likelihood for AD/HD diagnosis. We concluded from this study that the increased intake of a 'Western' diet increases the risk for ADHD diagnosis, whereas this risk is

seemingly reduced with increased levels of physical activity. Confirmatory data from sufficiently powered randomized trials of diet and physical activity intervention are now required to test if the relationships between diet, physical activity, and AD/HD are truly causal.

Funders of the project: Australian Rotary Health Research Fund.

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

Gina Ambrosini, Rae-Chi Huang, Trevor Mori, Beth Hands, Therese O'Sullivan, Nick de Klerk, Lawrence Beilin, Wendy Oddy.

The nutrition team is investigating the association of dietary factors with metabolic and depressive outcomes in a longitudinal model using data from the Raine Study Cohort. In the first part of this project Dr Ambrosini investigated the effect of dietary patterns on metabolic risk factors.

Overweight and other risk factors for cardiovascular disease (CVD) as well as their clustering, or the metabolic syndrome, are increasingly prevalent among children and adolescents. We examined dietary patterns, CVD risk factors, and the clustering of these risk factors, in a group of 14 year olds living in Western Australia. To do this, usual dietary intake was assessed with a food frequency questionnaire. Two dietary patterns,

'Western' and 'Healthy', were identified using factor analysis. Associations between these dietary patterns and BMI, waist circumference, systolic blood pressure, fasting levels of serum glucose, insulin, total cholesterol, HDL C, LDL C, triglycerides and insulin resistance were assessed using analysis of variance. Belonging to a high risk cluster for these risk factors was examined in relation to dietary patterns using logistic regression. Aerobic fitness and socio demographic factors were considered as potential confounders. Our results showed that 1,139 adolescents provided complete data. Higher 'Western' dietary pattern scores were associated with a greater odds of belonging to the high risk cluster (p for trend =0.02) and greater mean values for total cholesterol (p for trend=0.03), waist circumference (p for trend=0.03) and BMI (p for trend =0.02) in girls, but not boys. Scores for the 'Healthy' dietary pattern were not related to the high risk cluster but were inversely associated with serum glucose in boys and girls (p for trend=0.01 and 0.04 respectively) and were positively associated with HDL C in boys (p for trend=0.02). From this project we concluded that dietary patterns were associated with CVD risk factors and the clustering of these risk factors in adolescence.

Funders of the project: National Heart Foundation/Beyond Blue grant.

Dietary intake and food sources of fatty acids in Australian adolescents

Therese O'Sullivan, Gina Ambrosini, Lawrie Beilin, Trevor Mori, Wendy Oddy.

The nutrition team is investigating the intake of dietary fatty acids and their effects on health outcomes, using data from the Raine Study Cohort. In the first part of this project Dr O'Sullivan investigated the intake of dietary fatty acids from the cohort of adolescents. In the second part of this project Dr O'Sullivan is investigating essential fatty acid intake with blood pressure.

Dietary fat consumed during childhood and adolescence may be related to development of cardiovascular and other chronic diseases in adulthood, however there is a lack of information on specific fatty acid intakes and food sources in these populations. Our study aimed to assess fatty acid intakes in Australian adolescents, compare intakes with national guidelines and identify major food sources of fatty acids. The subjects were 822 male and female adolescents aged 13-15 years, participating in The Western Australian Pregnancy Cohort (Raine) Study, Perth, Western Australia. Dietary intake was assessed using measured three-day records. We found that mean daily total fat intakes were 90±25 g for boys and 73±20 g for girls, with saturated fat contributing 14% of total energy intake. Mean contribution to daily energy intake for linoleic (LA), alpha-linolenic (ALA), eicosapentaenoic (EPA), docosapentaenoic (DPA) and docosahexaenoic (DHA) acids were 3.0%, 0.40%, 0.02%, 0.01%, 0.04%, respectively, for boys, and 3.3%, 0.42%,

0.02%, 0.01%, 0.05%, respectively, for girls. To meet the guidelines for prevention of chronic disease, consumption of long-chain omega-3 fatty acids in this population needs to increase up to three-fold and the proportion of saturated fat decrease by one third. Girls were more likely to achieve the guidelines. Major food sources were dairy products for ALA, margarines for LA, and fish for long-chain omega-3 fatty acids. Our results suggest that for this population, a higher dietary intake of long-chain omega-3 fatty acids, particularly for boys, and lower proportion of saturated fat is required to meet recommendations for prevention of chronic disease.

Funders of the project: NHMRC Program Grant #353514.

Polyunsaturated fatty acid intake is inversely associated with blood pressure in adolescent boys

Therese O'Sullivan, Alexandra Bremner, Lawrie Beilin, Gina Ambrosini, Trevor Mori, Rae-Chi Huang, Wendy Oddy.

Dietary intake of fatty acids, particularly omega-3 fatty acids, may modify blood pressure, however the evidence is generally limited to middle-aged or hypertensive populations. The aim of this project was to examine cross sectional associations between blood pressure and fatty acid intakes in adolescents participating in the 14-year follow-up of The Western Australian Pregnancy Cohort (Raine) Study. Fatty acid intakes were assessed in 814 adolescents aged

13-15yrs using 3-day diet records and an updated fatty acid food composition database. Resting blood pressure was determined using multiple readings. In adjusted regression models, systolic blood pressure was inversely associated with intakes of total polyunsaturated (b=-0.436, P<0.01), omega-3 (b=-2.47, P=0.02), omega-6 (b=-0.362, P=0.04), and long chain omega-3 fatty acids (b=-4.37, P=0.04) in boys. Diastolic blood pressure and mean arterial pressure were inversely associated with intakes of long chain omega-3 fatty acids in boys only (b=-3.93, P=0.01, b=-4.05, P=0.01, respectively). For specific long chain omega-3 fatty acids, significant inverse associations were observed between eicosapentaenoic acid and docosahexaenoic acid with measures of blood pressure, but no significant associations were observed with docosapentaenoic acid. No significant associations were observed in girls, or with the omega-6 to omega-3 ratio. In conclusion, higher intakes of both omega-3, particularly long-chain, and omega-6 polyunsaturated fatty acids were significantly associated with lower blood pressure in adolescent boys, but not girls. Our results suggest that the relationships between dietary fatty acid intake and blood pressure in adolescents may be moderated by gender.

Funders of the project: NHMRC Program Grant #353514, Heart Foundation/Beyond Blue.

Long Term Mental Health and

Breastfeeding

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

The Nutrition team has shown that children who were breastfed for longer than six months had a lower risk of mental health problems as they entered their teen years. The research, led by Associate Professor Wendy Oddy, is in press in The Journal of Pediatrics and was picked up by Reuters new York to promote globally. This study is ground breaking because no other study has reported such associations and it has taken six years to get into print because the team were waiting for the data to be finalized.

Dr Oddy said breastfeeding for a longer duration (more than six months) appears to have significant benefits for the mental health of the child into adolescence. "There has been much evidence about the benefits of early breastfeeding, but the importance of this study is that it shows continued benefits from extended feeding," Dr Oddy said. "Given the rising prevalence of mental health problems, interventions to assist mothers to breastfeed, and to breastfeed for longer, could be of long term benefit to the community. "As with any of these types of studies, it should be stressed that the findings do not mean that individual children that weren't breastfed will have mental health problems, it's about lowering the risk at a population level."

The research team analysed data from more than 2000 children involved in

Western Australia's Raine Study. Just over half were breastfed for six months or longer, 38% percent were breastfed for less than six months, eleven percent were not breastfed. The participants undertook mental health assessments when they were 2, 5, 8, 10, and 14 years old. At each of the assessments, the researcher team found a link between breastfeeding duration and behaviour. For each additional month of breastfeeding, the behaviour score improved. This remained valid after adjustment for socio-economic, social and other factors impacting on parenting.

Dr Oddy said breastfeeding could help babies cope better with stress. "There are a number of ways extended breastfeeding could assist child development. We know that breast milk is packed full of nutrients that help with the rapid brain development that occurs in the early years. It might also signal a strong mother-child attachment and these benefits may last."

Funders of the project: NHMRC Program Grant #353514.

Antenatal and perinatal determinants of behaviour in childhood and adolescence: The Western Australian Pregnancy Cohort (Raine) Study

Monique Robinson, Wendy Oddy, Neil McLean.

This work has been conducted for Monique Robinson's MPsych/PhD candidature, a joint project between

the Telethon Institute for Child Health Research and the School of Psychology at The University of Western Australia. Using the Raine Study cohort, the project is an in-depth analysis of the early life origins of behavioural development, including the identification of antenatal maternal lifestyle risk factors for later child and adolescent behavioural problems. Studies within the project have examined the effect of maternal psychosocial stress during pregnancy, cigarette smoking, alcohol use and hypertensive diseases of pregnancy on later behavioural outcomes to adolescence. Five publications have resulted from the project to date.

Funders of the project: NHMRC Program Grant #353514.

Developing evidence-based recommendations for managing childhood obesity

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

This study aims to identify the factors that contribute to the development and persistence of overweight and obesity in children, as well as the factors that lead from overweight and obesity to the development of medical and psychosocial complications. Through the identification of such factors as well as a cost-analysis of the burden of overweight and obesity in children and a focus on the community aspects of childhood obesity we will be able to develop targeted, cost-effective and acceptable prevention and intervention

strategies. Ultimately, this will allow effective strategies to be chosen for a particular set of circumstances, rather than applying blanket prevention and intervention strategies that may not be successful and would use unnecessary resources.

The study currently consists of 1556 children who were weighed and measured at school, of which 470 are taking part in the medical/psychosocial assessment stage of the study. In addition to the children from the community there are currently 59 children recruited into the study from the Obesity Clinic at PMH. Of the total sample of children, there are 101 classified as obese, 140 classified as overweight and 279 classified as healthy weight.

Findings from the GAD Study have shown an increasing tendency to pathology with increasing degree of adiposity on a comprehensive range of psychological and biomedical measures in primary school aged children.

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

Investigating methods for managing childhood obesity

Lisa Gibson.

Currently there are no satisfactory treatment or prevention strategies for overweight and obese children. New treatment approaches to the management of childhood obesity are needed. This projects aims to develop, test and

disseminate a new intervention for childhood obesity. The approach is novel in that mothers will be the primary agents of change. There are several compelling reasons for this. Mothers play a critical role in shaping children's eating behaviours, and influence food choice through role modelling. It is likely that changes in the mother's eating and exercise habits will lead to a parallel change in the pre-pubertal child's eating and exercise behaviours.

Assessment protocols have been developed for the trial of the intervention program. These assessment protocols include self-report questionnaires and semi-structured interviews which will be administered to mothers and children both prior to commencing the intervention program and at completion of the intervention program.

The intervention program is based on a cognitive behavioural treatment (CBT) for obesity developed at the University of Oxford. The existing CBT has been now been modified for use with mothers of primary school children. Also, for the purposes of this project, modules focusing on parenting skills, educating parents about eating and exercise behaviours in children and promoting psychosocial wellbeing in children have been added to the original CBT. This intervention is now in the form of a manual for both participants and administrators.

At this stage it is anticipated that a trial of the intervention program will commence in 2010.

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

The Peel Study

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

Anne McMurray, Fiona Stanley, Barry Down, Phil Stumbles, Garth Kendall, Brendan Waddell, Margaret Simms, Peter Franklin, Anke van Eekelen, Jianghong Li, Eugene 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 onwards, 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. In 2009, recruitment efforts progressed: 160 families are currently participating and continued recruitment is based on 25 families/month.

Funders of the project: ARC Linkage funding (2007-2011).

Childhood Mortality

Western Australian Mortality Database for infants, children and young people:

Jane Freemantle, Anne Read, Nick DeKlerk, Kirsten Alpers, Margaret Woods, Peter Cosgrove, Ian Anderson, Fiona Stanley.

Work has continued on the database with mortality data now finalised for the years 2003, 2004 and 2005. Data for the year 2006 are partially collected. We now have almost a quarter of a century of comprehensive mortality information that describes the deaths of Western Australian born infants, children and young people. These 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.

The Department for Child Protection has entered into an agreement with the Institute to provide funding support for the continuation of the collection, classification, coding, validation and analysis of these data.

One of the main aims of the continuing development of this database is to provide comprehensive information that will enable development of targeted policy, community strategies and evidence-based initiatives to prevent deaths among WA children and young people. The database will also provide baseline data, including patterns and trends among Aboriginal and non-Aboriginal populations, from which to evaluate the effectiveness of interventions and policy development and implementation.

The WA Mortality Database is also being analysed to describe the comparative infant mortality in Australian Aboriginal, Alaskan Native, Canadian Métis and Maori infants. These analyses will be the first of their kind and have resulted from continuing collaborations with colleagues in Alaska, Canada and New Zealand.

Funders of the project: Department for Child Protection.

Centre for Developmental Health

Kate Taylor, Stephen Zubrick, David Lawrence.

The Centre for Developmental Health is an innovative research centre dedicated

to improving children's lives. It is a joint venture between the Telethon Institute for Child Health Research and Curtin University of Technology. Developmental health is an approach to health that seeks to understand determinants of optimal and suboptimal health and wellbeing across the lifespan. Optimal health and wellbeing outcomes include the absence of diseases and disorders and civic, social and economic participation in society. Suboptimal health and wellbeing outcomes include clinically defined diseases and disorders of childhood (e.g. otitis media, intellectual disability) and adverse developmental outcomes defined by society (e.g., school failure, contact with juvenile justice systems, and unemployment). It is well recognised that health and wellbeing trajectories are set early in life (e.g., low birth weight) and that societal risk factors (e.g., poverty) impose a greater threat to a society's human capability than diseases and developmental disorders. The Centre places a high priority on building research partnerships that bridge traditional discipline boundaries and expanding our post-doctoral capacity.

Australian Early Development Index

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

The Australian Early Development Index (AEDI) is a population measure

of young children's development. Like a census, it involves collecting information to help create a snapshot of children's development in communities across Australia. Teachers complete the checklist for children in their first year of full-time schooling. The AEDI measures five developmental domains:

- Physical health and wellbeing
- Social competence
- Emotional maturity
- Language and cognitive skills (school-based)
- Communication skills and general knowledge

The AEDI is based on the Canadian Early Development Instrument (EDI) which was developed by Dr Janus and Dr Offord at the Offord Centre for Child Studies, Mc Master University. In Australia, the Canadian EDI checklist was first trialed in the northern metropolitan suburbs of Perth in 2002 and 2003, with around 4,300 children. Since 2004 the adaption of the EDI - now called the Australian EDI, or AEDI has been carried out by the Centre for Community Child Health in partnership with the Telethon Institute for Child Health Research.

The Telethon Institute for Child Health Research has been primarily responsible for the technical adaptation and the scientific research and analyses of the development of the AEDI in Australia. A major piece of work has included the Indigenous adaptation of the AEDI with

a focus not just on the checklist itself but the associated teacher guidelines and the dissemination of AEDI results in Indigenous communities. The Indigenous AEDI adaptation study is jointly funded by Shell Australia and the Department of Education, Employment and Workplace Relations (DEEWR).

In 2009, the AEDI was completed nationwide for the first time with the Australian Government providing \$21.9 million for the implementation of the AEDI in recognition of the need for all communities to have information about early childhood development. Between 1 May and 31 July, information was collected on 261,203 children (97.5 per cent of the estimated national five-year-old population). This involved 15,528 teachers from 7423 Government, Catholic and Independent schools around Australia. The initial results (released in December 2009) provide a snapshot of the early childhood development outcomes for children in communities across Australia.

Funders of the project: The AEDI is conducted by the Centre for Community Child Health (at The Royal Children's Hospital, Melbourne and a key research centre of the Murdoch Children's Research Institute) in partnership with the Telethon Institute for Child Health Research, Perth. The national implementation of the AEDI is funded by the Australian Government Department of Education, Employment and Workplace Relations.

International Consortium for the Monitoring of Child Development.

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

As international interest and acknowledgment grows around the importance of monitoring child development various countries are looking for support in initiating monitoring activities. As such an International Consortium for the Monitoring of Child Development has been formed between the Offord Centre at McMaster University and the Human Early Learning Partnership in Canada along with the Telethon Institute for Child Health Research and the Centre for Community Child Health in Australia, with the WorldBank as a partner organisation. Currently the Institute for Child Health Research is involved in supporting Indonesia, Philippines, Jordan and Peru in their endeavors to adapt the EDI.

Funders of the project: Supported by: WorldBank, Van Leer Foundation and UNICEF.

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

Sven Silburn, Sue Ferguson-Hill, Roz Walker, Adele Austin, Jan Coe, Sally Brinkman.

Initiated in 2007, the Indigenous Australian Early Development Index (Indigenous-AEDI) project adapted the widely used Australian Early development Index (AEDI) to take into account Aboriginal

cultural differences in the influences on child development. The study was overseen by a National Indigenous AEDI Reference Group with input from Indigenous peak bodies and grass roots community organisations, parents, unions and government and non-government stakeholders throughout the project.

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

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

- The recommended use of Indigenous school personnel to work as cultural consultants with teachers in completing the AEDI checklists for Indigenous children.
- Modifications to the on-line teacher guide to provide additional information so that cultural considerations can be taken into account on certain checklist items.
- Additional checklist items of relevance to understanding the particular circumstances of Indigenous children. That may affect attendance and performance

(cultural, sickness or other); use of home language, history of otitis media or hearing difficulties.

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

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

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

The next stage of this adaptation study involves evaluation of the data on Australian Indigenous children gathered in different contexts across Australia by the national program and the development and publication of suitable community engagement and information dissemination processes for reporting AEDI findings back to communities in ways which are empowering and enabling effective local use of the data in advocating, planning and delivering services for Indigenous children and their families.

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

Silburn S, Brinkman S, Ferguson-Hill S, Styles I, Walker R, and Shepherd C. 2009 The Australian Early Development Index (AEDI) Indigenous Adaptation Study. Perth: Curtin University of Technology and Telethon Institute for Child Health Research. http://www.rch.org.au/aedi/about.cfm?doc_id=13283

Funders of the project: Funding through Shell Australia, Department of Families,

Community Services and Indigenous Affairs (Australian Government).

Starting on Track: The Pilbara AEDI Initiative

Roz Walker.

The Starting on Track project involved the implementation of the AEDI in Hedland and Newman and surrounding areas between Dec 2006 and Dec 2008. 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:

- baseline data on the strengths and vulnerabilities of pre-primary age children in across the Pilbara
- 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
- establishment of Early Years Action Groups
- reorientation of Communities for Children community partner programs in the West Pilbara; and

• direction to the BHP Billiton Iron Ore Community Investment Program 2010-2014

The focus of the project in 2009 was to develop culturally relevant materials to finalise the communication and dissemination of AEDI results to Indigenous communities in the Pilbara. This was undertaken in collaboration with Sue Ferguson Hill, coordinator of the Western Australian AEDI (Indigenous Adaptation)

Funders of the project BHP Billiton Iron Ore Health Partnership 2006-2009 & various sponsors.

Implementation and evaluation of the Australia Early Development Index (Indigenous adaptation) in the Western Desert communities BHP Billiton 2009-2014

Roz Walker.

The Telethon Institute for Child Health Research and BHP BIO have entered into a new partnership to support and evaluate the BHP Billiton Iron Ore's (BHPBIO's) Community Investment Program 2009-2014 which is focused on creating long term benefits for the Aboriginal communities in the Western Desert. The Community Investment Program 2009-2014 maternal and child health initiative for the Western Desert communities is largely based on the Australian Early Development Index (AEDI) Pilbara Community 2007 results from the 'Starting on Track' AEDI

implementation project. The initiative collected information across five developmental domains which measure early child development and school readiness. These domains include: Physical health and well-being; Social competence; Emotional maturity; Language and cognitive development; and, Communication skills and general knowledge. In 2008 the Institute/Kulunga also trialled the Indigenous-AEDI pilot project in these Western Desert communities. Both the AEDI 2007 and I-AEDI 2008 results for the Jigalong, Punmu, Parngurr and Koonawarrji communities confirm the critical need for a strategic focus on programs to improve early years outcomes for children 0-5 years as well as a reorientation of services to improve maternal health and early years development outcomes across all development domains. The 2008 I-AEDI results will be used as the baseline to measure improvements in early years development in Aboriginal in these communities over time.

The research project will use three key measures on an annual basis for five years to guide and evaluate BHPBIO's maternal and early child development initiative:

- 1) the implementation of the Australian Early Development Index (AEDI) (which now incorporates Indigenous elements);
- 2) the 0-5 years Aboriginal Health Schedule (Department of Health) recently reviewed by TICHHR; and,
- 3) existing maternal health indicators developed for the Overcoming Indigenous Disadvantage COAG initiatives. Together these measures will provide a robust evidence base to

inform and evaluate the new BHPBIO Aboriginal early child and maternal health initiative in Jigalong and other Western Desert communities. The project uses a community based action research process to implement and disseminate the AEDI results and trial the 0-5 Child Health Schedule to build community capacity and sustainability and improve maternal health and child development, education, health and wellbeing outcomes over the next five years.

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

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

confirm whether and in what ways there is a need for the reorientation of program support or strategic intervention in particular communities. The collection of data on an annual basis for 4, 5 and 6 year olds will provide school based profiles which will enable the schools to gauge shifts in developmental domains over time. This is a unique opportunity to provide fine grained monitoring and evaluation of the Community Investment Program 2009-2014.

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

Early Child Development, Program Evaluation

Randomised cluster control trial evaluating the impact of an Early Childhood Education and Development initiative across Indonesia

Sally Brinkman, Menno Pradhan, Amanda Beatty.

With a greater scale for improvement in school readiness outcomes, the evaluation of ECED programs in the developing countries affords a greater scope for investigation into the facilitators and barriers for success. This ECED program that we are evaluating represents a significant investment on behalf of the Republic of Indonesia and the World Bank.

With significant economic growth over the last 5 years, Indonesia is currently classified as a lower to middle income country. Despite this fact, there are over 35 million people living below the poverty line – representing 16% of the population. In addition it is estimated that up to half the population are vulnerable to poverty with the inequality between rich and poor vast. A large disparity in socio-economics, nutrition, education and health exist between districts, with infant and child mortality rates significantly higher in the poorer communities. In addition, children from the poorer villages start school later, complete fewer years of schooling and have higher drop out and repetition rates.

The objective of the Early Childhood

Education and Development program is to improve poor children's overall development and readiness for further education by (i) increasing the delivery of ECED services in targeted poor communities using a community-driven approach and (ii) developing a sustainable system for delivering ECED services. The project will reach approximately 738,000 children aged 0 to 6 and their parents/ caretakers living in about 6,000 poor communities (dusuns) located in 3,000 villages within 50 districts. Participating districts have been selected according to poverty level and their commitment to developing ECED services.

The outcomes of the research will enable us: to determine (if and to) what extent the ECED project improved children's development, attendance and readiness for school; to what extent the ECED project improved parental awareness and practices; if the project increased the availability and utilisation of ECED services and if so, how those impacts differed by gender, wealth, and level of service delivery at baseline. It is essential that the research will be able to determine what factors contributed to any success or failures by the ECED program. By including local academics in the research we will facilitate cultural relevance, local knowledge and contextual relevance to the research (instrument development, fieldwork nuances through to identification of key stakeholders etc). A well designed and implemented impact evaluation will provide a unique opportunity to inform the current and future practices in Indonesia and abroad. In

addition the evaluation will utilize outcome instrumentation that can be internationally referenced and thus rigorous piloting and cultural adaptation of internationally recognized instruments will be required.

The ADRA Grant has enabled the employment of two early career academics based at the University of Gadjadara (UGM) in Indonesia. As both academics are teaching university students, building their capacity, skills and knowledge will not only benefit themselves but their current and future students. There is a clear and recognised deficit in Indonesia in the knowledge and capacity regarding high quality research methods, research application, instrument development, statistical/analytical skills and the importance of good quality evaluations of programs (such as this ECED program) as well as simply a lack of understanding of the importance of early child development and education. Building local capacity will decrease the current reliance on “fly-in consultants”. Over the time of this research our aim is to ensure that Dr Elan Satriawan and Ms Amelia Malika will independently have the skills, knowledge and confidence to be able to design, undertake and manage such large scale research programs and have the confidence to disseminate the research findings to government, donors and other stakeholders including within the academic literature.

Funder of the project: Australian Development Research Award (ADRA) awarded by AusAid.

LOOKING at Language

Mabel Rice, Kate Taylor, Stephen Zubrick, Shelley Smith.

LOOKING at Language is a 10-year study (2002 – 2012) of language development and disorders in twins and singleton children funded by the National Institutes of Health (NIH). The study, known as LOOKING at Language, is an international collaboration between Professor Mabel Rice from the University of Kansas, Associate Professor Kate Taylor and Professor Stephen Zubrick from the Centre for Developmental Health and Professor Shelley Smith from the University of Nebraska Medical Center. We are investigating genetic and environmental influences on normal and impaired language acquisition in 1000 WA twin and singleton children at 2, 4, 6 and 9 years. Our focus is on possible genetically guided developmental timing effects, such that inherited mechanisms activate or are delayed at developmental transition times, across different dimensions of language, across language and reading phenotypes. The outcomes will be highly relevant for the identification of children at risk for language disorders and the estimation of possible genetic, environmental, and interactive age modulated effects on language acquisition and impairment and reading acquisition and impairment. Our early publications have shown that early language delay is governed far more by basic biological processes and process internal to the child than it is by environmental circumstances.

We established that one in five children with early language delay are at risk for language impairment at 7 years and that syntax and morphosyntax are the most vulnerable aspects of language for children with a history of early language delay. We are set to realize the publication opportunities from this study over the next few years when data from successive birth cohorts is available from each wave of follow-up (i.e., 2, 4, 6 and 9 years). The study provides a unique multidimensional population based longitudinal dataset for studying language acquisition, Specific Language Impairment, reading acquisition and reading impairment.

Funders of the project: U.S. National Institutes of Health.

Measuring and modelling the childhood determinants of human capital formation and human capability expansion

Stephen Zubrick, Sven Silburn, Denis Trewin, Ann Sanson, Bill Louden, David Lawrence.

This study uses archival data sources and data linkage capacities to focus on the measurement of human capability across the life course. Specifically the study aims to integrate archival data with population data registers in the health, education and social services sectors to study patterns of participation (or non-participation) associated with specific education, health and developmental burdens; and to use national data sources such as the Longitudinal Study of Australian Children

al compare and validate findings across settings.

Key research findings this year include:

- teenage pregnancy was found to be significantly associated with family type, highest school year completed by primary carer, combined carer income, whether the primary carer was a smoker and whether the girl displayed aggressive and delinquent behaviours during childhood and adolescence. Aggressive and delinquent behaviours were predictive of teen pregnancy even when observed at young ages.

- deliberate self-harm was found to be significantly associated with female sex, primary carer being a smoker, being in a step or blended family, having more emotional or behavioural problems than other children, living in a family with inconsistent parenting style, and having a teenage mother.

- people with common mental disorders such as anxiety or depression smoke at substantially higher rates than the remainder of the community, and represent about one-third of Adult smokers in Australia. People with these disorders are more likely to start smoking, less likely to quit, and smoke on average for longer duration. These people are less able to respond to the mainstream anti-smoking campaigns that have been successful in the broader population.

We have also published an overview of the conceptual framework of social skills as the candidate outcomes underpinning the

life course approach to human capability development, the causal mechanisms that prompt, facilitate or constrain their development, and the resources that potentially mediate or moderate these effects. Additionally work is ongoing to investigate the interaction between child temperament, parenting styles, and emotional and behavioural outcomes in children.

Funders of the project: Australian Research Council.

Restor(y)ing Aboriginal Parenting: Development and evaluation of a culturally relevant program to support Aboriginal parents promoting their children's behavioural and social competence and readiness for school learning

Stephen Zubrick, Sven Silburn, Rob Donovan, Helen Milroy, Jill Milroy, Ted Wilkes, David Lawrence, Heather D'Antoine, Cheryl Kickett-Tucker, Dawn Bessarab, Adele Cox .

Our objective is to develop, implement and evaluate a culturally relevant program for parents of Aboriginal children to reduce child social, emotional and behavioural problems. The program aims to: a) address family issues of intergenerational grief and loss, b) build parents' confidence and skills in parenting, c) supports the development of children's adaptive behaviours, d) strengthens positive identification with Aboriginal culture, and prepare children for successful transition to school.

We have developed and named the program 'Too Solid'. We have completed the second year of trialing 'Too Solid' and the fourth year of the project. We have demonstrated that trained staff are able to sustain delivery of the 'Too Solid' intervention via community based agencies. We will spend this year, the final year of the p

roject, analyzing the data and finalizing the products that have been produced for 'Too Solid'.

Funders of the project. NHMRC Grant #323242

Social determinants of child health/social epidemiology

Parental work hours and quality of diet in adolescents

Jianghong Li, Wendy Oddy, Therese O'Sullivan, Gina Ambrosini.

The study investigates the association of mother's and fathers' work hours and other socioeconomic factors with diet quality in a cohort of adolescents followed from pregnancy to age 13 in Western Australia (the Raine Study), using a diet quality index and dietary patterns developed at the Institute for Child Health Research.

Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation

Research Institute, Centre for Developmental Health, Curtin University.

Parental work and child mental health

Jianghong Li, Garth Kendall, Lyndall Strazdins, Mike Dockery, Sonia Andrews, Sarah Johnson.

The project aims to investigate the impact of parental employment status and non-standard work schedules on the mental health and wellbeing in Australian children/ adolescents and to shed new light on the social and economic causes of the high prevalence of mental health problems in today's children. The proposed research will be based on data from Longitudinal Study of Australian Children (LSAC) and the Western Australian Pregnancy Cohort Study (Raine). The project draws on multidisciplinary expertise from sociology, social epidemiology, developmental epidemiology, clinical psychology and labour economy. We have conducted a comprehensive review of the literature on non-standard work schedule and child mental health and behavioural problems and the review will inform specific research aims and questions. We anticipate two PhD students to come on board in 2010. We also have a pending grant application whose outcome will be announced in June 2009.

Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for

Developmental Health, Curtin University.

Breast feeding duration and school achievement in Grade Five

Wendy Oddy, Jianghong Li, Stephen Zubrick, Andrew Whitehouse, Eva Malacova.

This project investigates the effect of breastfeeding duration on numeracy and literacy in a subset of the Raine Cohort children in grade 5 who attended government school in WA, independent of parental socioeconomic and demographic characteristics and home stimulation. The study further examines gender differences in the effect of breastfeeding on numeracy and literacy attainment.

Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

Maternal stressful events in pregnancy and numeracy and literacy at grade 5

Jianghong Li, Anke van Eekelen, Monique Robinson, Jonathan Foster.

This study examines the timing and number of stressful events in pregnancy and their link with numeracy and literacy achievement in a subset of the Raine Cohort children in grade 5 who attended government schools in WA. The aim of the study is also to demonstrate the

importance of examining gender difference in the impact of maternal stressful events in pregnancy on offspring's school achievement and to elucidate the need to distinguish between confounding factors from mediating factors in the causal pathway.

Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

HIV vulnerability in out-of-school adolescents and youth in Yunnan, China

Lijun Yang, Jianghong Li.

This is a UNICEF funded project based in China and I am a collaborator on the project. The project aims to understand the level of knowledge about HIV transmission and prevention and risk taking behaviours in a random sample of out-of-school adolescents in Yunnan Province. Cross-sectional data has been collected and the project is at the stage of analysis.

Funders of the project: Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University

The Raine Study

The Raine Study

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

Raine Study Secretariat

Scientific Director: Assoc Prof Craig Pennell, Study Manager: Ms Jenny Mountain, Data Manager: Dr Louise McKenzie

Raine Study Cohort Co-ordination: Diane Wood, Alex Baptista D'Vauz, Emilly Hockley, Tegan Grace, Allison Shorten, Suzanne Greene, Denny Craig,Carolynn Smargiassi, Amy Lee.

Website: www.rainestudy.org.au

The Western Australian Pregnancy (Raine) Cohort Study in a longitudinal cohort study. The Raine Study Cohort was established between 1989 and 1991 to determine how events during pregnancy and childhood influence health in later life. 2900 pregnant women entered the study and 2868 live births were recruited into the cohort. The Raine Study cohort has been followed closely over the last 18 years by a collaborative team of researchers. Follow up assessment of the cohort was done at birth, 1, 2, 3, 5, 8, 10, 14, 17 and 18 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 study families are broadly representative of the Western Australian population. The Raine study is an invaluable resource for Western Australian Researchers. There

are currently more than 60 researchers utilising more than 6000 variables available on each member of the Raine cohort. The investigators study 18 broad areas of research including: asthma and allergy, cardiovascular, cognitive neuroscience, dental health, developmental origins of health and disease, eating disorders, epigenetics, gastro-intestinal, genetic epidemiology, growth & nutrition, infectious disease/immune response, language and social development, mental health, musculo skeletal, physical activity, pregnancy and birth, reproductive health and risk taking behaviour. There is growing collaborative research between Raine study principle investigators. National and international research collaborations with the Raine study are continuing to develop.

2009 saw the completion of the 17 year old follow up of the cohort. 1258 teenagers came to the Institute and completed an intensive 5 to 6 hour follow up. In addition to this, they completed a comprehensive questionnaire, a food frequency questionnaire, provided a blood sample, completed a seven day activity diary whilst wearing a pedometer and some participants wore a 24 hour blood pressure monitor. We applaud their commitment to the Raine Study. Organisation of the next cohort follow up at 20 years of age was done in 2009. This study will concentrate on eye health and commence in 2010.

A Community Conversations Evening was held in September. This provided a forum for interaction between Raine

Study Participants and investigators. The objective of the evening was to obtain the participants' perspectives on priorities for research within the Raine Study. It was a very productive and enjoyable evening. In general the participants wanted more feedback, were genuinely interested in DNA research and were happy to provide DNA and saw mental health, bullying, reproduction and fertility as important research areas.

The very successful and enjoyable Annual Raine Study Scientific Meeting was held in December with 20 scientific presentations from Raine Study Investigators. Over 60 people attended the day and a booklet containing over 65 abstracts was compiled.

In 2009 25 papers were published by Raine Study Investigators. Three NH&MRC and one CIHR grant applications were successful.

In 2009 The Raine Study Secretariat were successful in obtaining funding commitment for Raine Study Core Cohort Management from the collaborative Institutions involved in the Raine Study and wish to thank the Telethon Institute for Child Health Research, The University of Western Australia, The Women and Infants Research Foundation at King Edward Memorial Hospital, The UWA Faculty of Medicine, Dentistry and Health Sciences and the Raine Medical Research Foundation who have again generously committed funds to the continuation of the Raine Study.

In 2009 the Raine Study was supported by: The Australian Arthritis Foundation;

The Gastroenterology Society of Australia; NH&MRC 403981, 458623, 403968, 572613; NH&MRC 353514 (Stanley et al program grant); National Heart Foundation; Rotary Health Research; Canadian Institute of Health Research; Women's and Infants Research Foundation; The Faculty of Medicine and Dentistry and Health Sciences, UWA

Child Nutrition and Development (The Raine Study)

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

Associate Professor 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, Associate Professor 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 Fund

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

Associate Professor 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 aims 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 2009, we completed collecting (i) data in the field of mental health and cognitive and neuroendocrine development as part of the Raine Study follow up at 17 years of age. Our collection of data on stress responsiveness using the Trier Social Stress Test in the Raine Study at 18 years of age is still in progress with nearly 1000 participants tested by the end of 2009. In addition, our fMRI sub-study to image the functional circuitry underlying cognition and execution in late adolescence has started in 2009 in collaboration with the MRI Research Unit at Fremantle Hospital.

NHMRC (2007-2009, with an extension to 2010 to complete fMRI) / Women and Infants Research Foundation of Western Australia (WIRF; 2006-2008) / Canadian Institutes of Health Research (CIHR; 2007-2010),

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

Professor Martha Hickey, Dr Eugen Mattes, Professor Jeff Keelan, Dr Andrew Whitehouse, A/Professor Jonathan Foster, Professor John Newnham

Aim: To define the prospective

association between prenatal androgen exposure and specific mental health and language development in childhood and adolescence.

Hypothesis: Prenatal androgen exposure alters early life brain development and impacts on subsequent mental health and language development.

Background

The developing brain is highly androgen sensitive. Small studies suggest that raised prenatal androgens influence subsequent mental health and language development. However, this has previously been tested in large prospective studies of normal pregnancy

Methods

We are using the Raine Study where we have biological samples to measure the concentrations of key bioactive androgens in stored maternal plasma and umbilical cord plasma along with extensive mental health and language development measures taken at age 1, 2, 3, 6, 8, 10, 13 and 16 years. We will examine the association between androgen levels and:

a. childhood mental health problems: specifically internalising and externalising problems

b. Developmental language difficulties

Using extensive existing data to take into consideration other key variable likely to influence these outcomes

Outcomes and significance

Mental health disorders and developmental language difficulties are prevalent and commonly present in childhood. This rare, prospective cohort will be the first study to prospectively link prenatal androgen exposure in normal pregnancy with mental health and language outcomes in childhood and adolescence. These studies may reveal novel pathways underlying common disorders of mental health and language development, leading to tests to identify those at risk in early life, interventions to reduce prenatal androgen exposure and facilitate early intervention to prevent adverse outcomes in later life.

Funding. This project has been funded by Australian Rotary Health Research Fund (2008-2009). Applications to NIH (NIMH) and to NHMRC are under consideration

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, Prof Peter O'Sullivan, Dr Anne Smith, Dr Andrew Briggs, Dr Garth Kendall, Dr Amity Campbell, Dr Darren Beales, Dr Clare Pollock, Dr Clare Rees, Dr Melissa Davis

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, socioeconomic status) domains on the development of spinal pain.

To date 13 journal papers have been published/accepted, with 9 more currently in review and a further 10 in preparation. A number of presentations have also been made at national and international conferences.

NHMRC: Project Grant 323200 2005-2009

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

Assoc Prof Leon Adams, Prof John Olynyk, 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 underwent a liver ultrasound during their 16/17 follow up assessment.

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 Eekelen, Assoc Prof Craig Pennell, Prof John Newnham, Prof Steven Lye, Prof Fiona Stanley

The objective of this project is to define stress-induced activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis in late adolescence as an outcome of childhood development in the Raine Study participants. At 18 years of age, their biological response to an acute psycho-social stressor (Trier Social Stress Test) is measured by analyzing the levels of ACTH and cortisol in blood and saliva collected before and after the stressful experience. This test helps to better understand 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 also aim to identify polymorphisms within genes that regulate the function of the HPA axis in the children and their parents within the Raine cohort. These data complement the stress response data and improve analysis of 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)

Professor Martha Hickey, Professor Roger Hart, Dr Deb Sloboda, Professor Dorota Doherty, Professor Steve Franks

NHMRC 403968 (2006-09): The Fetal and Early Childhood Origins of the Polycystic Ovary Syndrome (PCOS): A Prospective Cohort Study

PCOS is the most common endocrine disorder in women. The origins of PCOS are unknown, but animal and small human studies suggest that PCOS may arise due to elevated prenatal androgen exposure. This hypothesis has not previously been tested in large prospective studies of normal pregnancy. This study aimed to test this hypothesis in the Raine Cohort using archived maternal and umbilical cord biological samples. Participation was demanding for these adolescents, requiring attendance on day 2-5 of menstrual cycle for ultrasound, blood tests and examination. Nevertheless, we recruited

over 250 girls and successfully addressed all our study aims. We have demonstrated that androgens can successfully be measured in these archived samples.

Our principal finding was that prenatal androgen exposure within the normal range did not predict PCOS in adolescence. Although a negative observation, this has received extensive interest from the endocrine community, since it rejects a widely-held hypothesis. Our findings were published in the prestigious *J Clin Endocrinol Metab* (JCEM: IF 6.325) and were the subject of an editorial (early origins of PCOS, hypotheses may change without notice de Zegher F, Ibáñez L. *JCEM*.2009;94(10):3682-5) which considered that our findings had led to a paradigm shift understanding the origins of PCOS. CIA Hickey was invited to present these data as a plenary lecture at the 14th World Congress of Gynecological Endocrinology in Florence in 2010. Data have also been presented at SGI in Glasgow 2009, ESHRE in Prague 2009 (prize for best presentation), the international DOHaD meeting in 2009 and the Australasian Fertility Society meeting in 2009. This illustrates the value of the Raine cohort in addressing key hypotheses concerning the influence of early life events on later life health that cannot be addressed in other populations.

In addition, we have generated new and clinically important data concerning the prevalence and diagnostic features of adolescent PCOS, early life factors

regulating reproductive function in females and the relationship between prenatal androgens and brain growth. Further, we have shown that digit ratio does not reflect prenatal androgen exposure females.

PUBLICATIONS ARISING

1. Hart R, Sloboda DM, Doherty DA, Norman RJ, Atkinson HC, Newnham JP, Dickinson JE, Hickey M. Circulating maternal testosterone concentrations at 18 weeks of gestation predict AMH in adolescence: *Fertil Steril*. 2010 Feb 13. [Epub ahead of print] (IF 4.167)
2. Hart R, Doherty DA, Norman RJ, Franks S, Dickinson JE, Hickey M*, Sloboda DM* (joint senior). Serum AMH levels are elevated in PCO and PCOS *Fertil Steril*. 2010 Jan 6.
3. Whitehouse AJ, Maybery MT, Hart R, Sloboda DM, Stanley FJ, Newnham JP, Hickey M. Free testosterone levels in cord blood predict infant head circumference in females. *Dev Med Child Neurol*. Accepted Jan 2010 (IF 2.561)
4. Hart R, Sloboda DM, Doherty DA, Norman RJ, Atkinson HC, Newnham JP, Dickinson JE, Hickey M. Prenatal determinants of uterine volume and ovarian reserve. *JCEM* 2009; 94(12):4931-7 (IF 6.325)
5. Hickey M et al; The relationship between maternal and umbilical cord androgen levels and PCOS in adolescence: *JCEM* 2009 Oct;94(10):3714-20. (IF 6.325)
6. Sloboda DM, Hart R, Hickey M. Developmental Origins of Reproductive

Health. In Newnham JP, Ross MG (eds): *Early Life Origins of Human Health and Disease*. Karger, 2009: 113-123

7. Hickey M, Doherty DA, Hart R, Norman RJ, Mattes E, Atkinson HC, Sloboda DM. Maternal and umbilical cord androgen concentrations do not predict digit ratio (2D:4D) in girls: a prospective cohort study. *Psychoneuroendocrinology*. Accepted Feb 2010 (IF 3.788)

Genetic Epidemiology and the Genome Wide Association Scan (the Raine Study)

Assoc Prof Craig Pennell, Prof Lyle Palmer, Prof George Davey-Smith Prof John Newnham, Prof Lawrie Beilin, Prof Fiona Stanley, Prof Nick de Klerk, Prof Steve Zubrick et al

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.

DNA collected from the Raine study members is being utilized for genotyping for 600K SNPs across the human genome. The five specific phenotypes that will be investigated in this study include: 1) HPA-axis dysfunction; 2) obesity and growth trajectories; 3) metabolic syndrome phenotype; 4) cardiovascular dysfunction; and 5) anxiety/depression. These phenotypes have been selected because all have previously been demonstrated to be associated with sub-optimal antenatal and postnatal environments in human and animal studies.

NHMRC Project Grant 572613

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.

Funding: Healthway

Antenatal and perinatal determinants of behaviour in childhood and adolescence: The Western Australian Pregnancy Cohort (Raine) Study.

Monique Robinson PhD candidate, Assoc Prof Wendy Oddy, Prof Neil McLean : Prof John Newnham, Mr Peter Jacoby, Prof Nick de Klerk, Professor Fiona Stanley, Assoc Prof Craig Pennell, Dr Anke van Eekelen, Prof Sven Silburn, Prof Steve Zubrick, Dr Eugen Mattes, Assoc Prof Garth Kendall,...

This work has been conducted for Monique Robinson's MPsych/PhD candidature, a joint project between the Telethon Institute for Child Health Research and the School of Psychology at The University of Western Australia. Using the Raine Study cohort, the project is an in-depth analysis of the early life origins of behavioural development, including the identification of antenatal maternal lifestyle risk factors for later child and adolescent behavioural problems. Studies within the project have examined the effect of maternal psychosocial stress during pregnancy, cigarette smoking, alcohol use and hypertensive diseases of pregnancy on later behavioural outcomes to adolescence. Five publications have resulted from the project to date.

NH&MRC Programme Grant

Suicide Prevention

Suicide prevention research and translation project

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

The Institute's program of translational research in suicide prevention aims to ensure current policy and practice for the prevention of suicide and suicidal behaviour is informed by current scientific knowledge. The Institute also 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.

In September 2009, the Ministerial Council for Suicide Prevention was re-convened with a new membership, the WA State Suicide Prevention Strategy 2009-2013 was launched by the Minister for Mental Health and Expressions of Interest were called to manage the implementation of the \$15 million Strategy. TICHR was selected as the Preferred Provider to manage the implementation of the Strategy and is currently negotiating with the Mental Health Division and the Ministerial Council for Suicide Prevention regarding the particulars of the business plan.

Funders of the project: Mental Health Division, Western Australian Department of Health.

Integrated proactive suicide bereavement postvention project

Brian English, Shawn Phillips, Sharon Hillman, Larina Bromley, Phil Riseborough, Kristy Staples, Karen Ugle, Belle Glassen, Stephen Zubrick.

The ARBOR (Active Response Bereavement OutReach) Project has been extended to 30 June 2011 to enable a more comprehensive longitudinal study of the impact and outcomes of the services provided for those bereaved by suicide in the Perth Metropolitan area. The service offers Peer Support (volunteers bereaved by suicide who are trained to support those newly bereaved), short term counselling, home visits and groups. Evaluation of the service is being undertaken by Edith Cowan University with a comprehensive plan of evaluating the interagency collaborations that assisted in the development and delivery of the service, qualitative and quantitative data collection on wellbeing outcomes of clients and evaluation of the impact of being involved in the service for the Peer Supporter volunteers.

Funders of the project: Commonwealth Department of Health and Ageing.

Staff and Students

Head of Division

Professor Steve Zubrick, MSc, MA, PhD

Kulunga Research Network Manager

Glenn Pearson, BA (Education)

Head of Epidemiology

Clinical Prof. Carol Bower, MBBS, MSc, PhD, FAFPHM, DLSHTM, FPHAA

Head of Biostatistics and Genetic Epidemiology

Professor Nick de Klerk, BSc, MSc, PhD

Research Staff

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Karina Allen

Kirsten Alpers

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Alison Anderson, BSc (Hons), GradDipPH

Helen Bailey, BSc (Nursing), MPH

Dr Stephen Ball, BSc (Hons), PhD

Gail Barrow, TC, Dip Teach, BAppSc (ACMD)

Jason Barrow, Cert IV in Indigenous Leadership

Ami Bebbington, BSc (Hons)

Lisa Bennett, BSc (Nutrition & Sports Science)

Melinda Berinson BSc (Hons) MPH

Anke Bergmann, Nurse, MPH

Assoc.Prof Eve Blair, BSc (Hons), PhD (Chem), PhD (MedSci)

Amy Blanket

Deborah Blumberg, MBCh

Kylie Blurton

Nancy-Lee Boulton

Jenny Bourke, BE, MPH

Hollie Bowker, OCCTher

Terry Boyle, BSc(Hons)

Sally Brinkman, BA, MPH

Anja Brok, BSW

Larina Bromley, BA(SocSc), PostGradDip(HlthProm), M HlthCouns

Jessinta Brown, BSc

Dr Susan Byrne, DPhil(Oxon), MPsych, PhD, BSc(Hons), DipEd BA (Hons), NHMRC Research Fellow

Bradley Calamel, BPsych, PGradDipEd. (School Psych)

Dr Anna Callan, BSc, M Res, PhD

Dr Phillippa Carter, MBBS

Suliat Chong

Ace Choo, BSc (Biomedical Science), MID(Tropical Infectious Diseases)

Daniel Christenson, BAPsych(Hons)

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Jennifer Cole

Troy Collard

Lyn Colvin, BCom, MPH

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Peter Cosgrove, BSc

Adele Cox, Dip(Broadcasting and Journalism)

Denny Craig, DipSecStudies

Heather D'Antoine, BApp Sci (HlthSci), M Hlth Econ (AbHlth)

Somer Dawson, BEcons, BHlth Sci(Hons)

Daniel de Klerk

Michelle de Klerk

Jan De Groot, BAppSci (MedTech), MPH

Aditya Deshpande, Bachelor of Dental Surgery

Tanya Dickson, BSc

Tahni Dingo

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Dr Jenny Downs, BAppSci (physio), MSc, PhD

Katrina Duncan

Paula Dyke, BAppS (Physio), MPH

Alex D'Vauz, BSc (Hons)

Courtney Eades

Francine Eades, Dip AppSci(Nursing), Master Applied Epi(ANU)

Tracy-Lee Edwards, Dip(PR)

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Jenny Fairthorne, MSc

Stephanie Fehr, BSc

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Melanie Fitzgerald

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Jennifer Gaudie, BCom

Nikki George

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Ron Gidgup

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Dr Rebecca Glauert, BPsych(Hons), PhD

Jackie Goldfinch

Girard Good

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Suzanne Green, REN, Phleb

Kristen Haas, BA

Jennifer Hafekost, BSocialSci

Katherine Hafekost, BSc(Hons)
Dr Erika Hagemann, BSc(Speech and Hearing Science)Hons, PhD, CPSP
Jessica Hall, B.Psych
Ann Hanning
Dr Janice Hansen, MPH, BSc(Hons), PhD
Michèle Hansen, MPH, BSc
Cara Harris
Tania Harris
Jarrod Hayden
Dr Tamika Heiden, BSc(Hons), PhD
Hilary Hii, BSc(Hons)
Sharon Hillman, B Psych, AMAPS
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Georgina Hollingsworth, BSc
Derry Houston, BA/MSocWk
Amber Howard, MPsych(Clinical)
Anna Hunt, BEdu
Tanyana Jackiewicz, BSc(Hons) MPH
Lorili Jacobs
Peter Jacoby, BA(Hons), MSc
Dr Le Jian, MBBS, PhD
Sarah Johnson, Bach of Arts (Psychology)
Candice Jolly
Michele Kerman
Dr Cheryl Kickett-Tucker, PhD
Marie King

Dr Ingrid Laing, BSc , PhD
Dr Amanda Langridge, BSc(Math.Sci), BSc(Hons), PhD
Assoc.Prof. David Lawrence, BSc, PhD, ATCL
Jessica Lee, BSc
Assoc. Prof. Deborah Lehmann, MBBS, MSc
Dr Jianghong Li, BA, MSc, PhD
Assoc. Clin. Prof. Helen Leonard, MBChB, MPH
Melissa Lynch
Sarah MacDermott
Patricia MacPherson-Walsh
Dr Eva Malacova, BSc (Hons), MSc (Applied Statistics), PhD
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Jacqueline Mansour, BSc, MPH
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Andrew Milne

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Dr Nusrat Naseem MBBS, MPH
Cathrine Nemer
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Serena O'Neil
Dr Colleen O'Leary, RN, BSc, MPH, PhD

Dr Therese O'Sullivan, BAppSci(HMS), BHlthSci(Nut.Diet), APD, PhD
Ashleigh Owen, BA
Michelle Parfitt
Jan Payne, SRN(UKCC),,PGradDip(Hlth Admin), MSc(Pub Hlth)
Dr Anne Pederson
Carol Philippe, RN
Shawn Phillips, BTh, MSWAP
Alani Pike, TA EDWA
Narelle Pryer
Anne Pugh
Belinda Quartermaine
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Dr Kate Riddell, PhD
Phil Riseborough, B.Psych ,M.Soc.
Deborah Robertson, BA, DipEd, Mphil
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Elke Scheepers, BA, AdvCert Tvl Cons
Dr Claire Scrine, BA(Hons), PhD
Carrington Shepherd, BA (Econs)
Dr Adeleh Shirangi, PhD
Allison Shorten, BSc (Hons)
Dr Rachel Skoss, PhD
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Grant Smith, BPsych, M Psych

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 Grad Dip HN
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 Amy Yates

Postgraduate Students

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 Aveni Haynes, Masters/PhD candidate,
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 Katrina Hopkins, PhD candidate, Curtin
 Rae-Chi Huang, PhD candidate, UWA
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 Amanda Jefferson, BSc, PhD candidate,
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 UWA
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 Kellie Jones, PhD candidate, ECU
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 Sandra Louise, PhD candidate, UWA
 Sarah Love, PhD candidate, UWA

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 Nevada Pingault, BSc (MedSci)(Hons I)
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 William Pomat, BSc (Hons), MSc, PhD
 candidate, UWA
 Monique Robinson, BA(Hons)Psych, PhD
 candidate, UWA
 Carrington Shepherd, BSc, PhD candidate,
 Curtin
 Desiree Silva, MB, BS, FRACP, MPH, PhD
 candidate, UWA
 Jessica Simons, PhD candidate, UWA

Lydia Sung, PhD candidate, UWA

S Van-Oyen, PhD candidate, UWA

Paula Wyndow, BSc Postgraduate Diploma,
PhD candidate, Curtin

Research Support

Helen Daley

Leanne Scott

Kathryn Wilson

Theses passed

Karina Allen, PhD, University of Western Australia: The Development and Maintenance of Cognitive and Behavioural Eating Disorder Symptoms.

Elizabeth Cromie, MPH, Determinants of breastfeeding duration related to residential isolation in mothers of West Australian Aboriginal Child Health Survey (WAACHS) participants

Kitty-Rose Foley, "Longitudinal Video Analysis of Gross Motor Abilities of Girls and Women with Rett Syndrome" BSc (Occupational Therapy) First Class Honours.

Amber Howard, M Clin Psych. Dietary patterns, Attention-Deficit/Hyperactivity Disorder (AD/HD), and clinical inattention in a cohort of Western Australian adolescents.

Amanda Langridge, PhD University of

Western Australia: Social and racial inequalities in birth rates and infant outcomes in Western Australia.

Sarah Love, PhD, University of Western Australia: The effect of botulinum toxin-A on the functional ability of young children with spastic hemiplegia due to cerebral palsy.

Melissa O'Donnell, PhD University of Western Australia: Towards Prevention – A Public Health Approach to Child Abuse and Neglect: Health Indicators and the Identification of Antecedent Causal Pathways.

Eva Malacova, PhD University of Western Australia: Developmental Pathways to Childhood Literacy and Numeracy: The Role of Early Health.

Alinta Oates, "Leisure participation for School-aged Children with Down Syndrome" BSc (Occupational Therapy) First Class Honours.

Colleen O'Leary, PhD, University of WA, with Distinction. Alcohol and pregnancy: policy, classification and fetal effects.

M.A. Smith; PhD, UWA: Glucose modulation of verbal episodic memory in adolescence.

Kelly Thomas, "Changes over time in medical conditions and service use by children with Down syndrome" BSc (Occupational Therapy) First Class Honours.

Anna Urbanowicz, "An analysis of use of equipment and respite services by families

with Rett syndrome." BSc (Occupational Therapy) First Class Honours.

Awards

Lyn Colvin. Australian Postgraduate Award (2006-).

Lyn Colvin. UWA Research Student Training Award (2009).

Jan de Groot. Cerebral Palsy Foundation: Promising Researcher Award, 3rd International Cerebral Palsy Conference, Sydney, Feb 2009.

Heather D'Antoine. Public Health Association of Australia (WA Branch) Indigenous Award, 2009.

Somer Dawson. Alessandra Lisi Memorial Prize, awarded by the Executive Committee of the International Clearinghouse for Birth Defects Surveillance and Research, 2009.

Francine Eades. Aboriginal Health College, Sydney. Diploma of Business (Management), 2009.

Francine Eades. Australian Institute of Company Directors', Company Director's Course – Certificate of attendance, 2009.

Noula Gibson. The HESTA Super Fund Contribution to the Profession Award, Australian Physiotherapy Association (WA Branch), November 2009.

Michele Hansen. Highly Commended Scientific Publication, Louisa Alessandri Memorial Fund, 2009.

Ingrid Laing. TSANZ/Japanese Respiratory Society Early Career Development Award, 2009.

Ingrid Laing. TSANZ Peter Phelan Paediatric Travel Grant, 2009.

Helen Leonard. Senior Research Fellow, National Health & Medical Research Council, 2009-2013.

Sarah Love. Best paper presentation: Allied Health, Laboratory and Pharmacy sessions, Research and Advances Seminar, PMH, October 2009.

Sarah Love. Invited lead author of "International consensus statement on the use of botulinum toxin-A in the paediatric lower limb", 2009.

Sarah Love. Mark Liveris Prize for the best higher degree student's project to represent the School of Physiotherapy, Faculty of Health Sciences, CUT, 2009.

Eva Malacova. UWA PhD Completion Scholarship, 2009.

Sarah McIntyre. Prize for Excellence, Annual Postgraduate Student Conference, Faculty of Medicine, School of Paediatrics and Child Health, 2009.

Kate Miller. Kim Adey and Nikki George, Curtin University of Technology Mental Health Research and Education Award, 2009.

Hannah Moore. GlaxoSmithKline (GSK) Australia Post Graduate Support Grant, 2009.

Hannah Moore. Director's Prize for Best Abstract, Telethon Institute for Child Health Research Postgraduate Student Forum, 2009.

Hannah Moore. Speakers Award, Statistical Society of Australia Western Australian Young Statisticians Workshop, 2009.

Melissa O'Donnell. Louisa Alessandri Award for Scientific Publication, 2009 .

Melissa O'Donnell. UWA PhD Completion Scholarship, 2009.

Melissa O'Donnell. Perron Award for Academic Achievement, 2009.

Colleen O'Leary. NHMRC Post-doctoral Training Fellowship. "Mothers with an Alcohol-Related Diagnosis in Western Australia 1983-2007: The impact on the health and use of health services of the mother and her offspring", 2010-2013.

Colleen O'Leary. Convocation Postgraduate Research Travel Award to attend 3rd International Conference on FASD in Victoria Canada, 2009.

Colleen O'Leary. Friends of the Institute, Travel Award to attend conference - Exploiting existing data for health research - in St. Andrews Scotland and the 1st International Symposium of SAF France, Paris, 2009.

Therese O'Sullivan. Overseas Conference Travel Award from Friends of the Institute (Telethon Institute for Child Health Research, 2009.

Therese O'Sullivan. Dietitian's Association of Australia's Emerging Researcher, 2009

Jan Payne. Friends of the Institute Travel Award. Conference attendance - 3rd International K. Conference on Fetal Alcohol Spectrum Disorder: Integrating Research, Policy and Promising Practice Around the World: A Catalyst for Change. Victoria, British Columbia, Canada, March 2009.

Jan Payne. The University of Western Australia, Graduate Research School, Graduate Research Student Travel Award. Conference attendance - 3rd International Conference on Fetal Alcohol Spectrum Disorder: Integrating Research, Policy and Promising Practice Around the World: A Catalyst for Change. Victoria, British Columbia, Canada, March 2009.

Jan Payne. Telethon Institute for Child Health Research Consumer and Community Advisory Council Participation Award. Inaugural recipient, December, 2009.

Glenn Pearson. UWA Post Graduate Indigenous Top up scholarship award, 2009.

Gavin Pereira. Australia Chinese Association for Biomedical Sciences travel award, 2009.

Gavin Pereira. Australian Postgraduate Award, 2009.

Gavin Pereira. CRC for Asthma and Airways top-up award, 2009.

Gavin Pereira. Stan and Jean Perron top-up award, 2009.

Monique Robinson. Australian Postgraduate Award, 2007-2009.

Monique Robinson. The Stan and Jean Perron Award, 2007-2009.

Monique Robinson. The Stan and Jean Perron Award to Recognise Exceptional Performance by a Research Higher Degree Student in 2008, 2009.

Monique Robinson. The Heinz Berendes International Travel Award, Society for Pediatric and Perinatal Epidemiologic Research (SPER), 2009.

Monique Robinson. UWA Prize for Higher Degree by Research Achievement (Special Commendation), 2009.

Katie Suriano. National Heart Foundation's Bendat Family Foundation Scholarship, April 2009.

R. Walker. Nominated for the Louisa Alessandri Award of Excellence in Research, Telethon Institute for Child Health Research, 2009.

External Committees

International

Eve Blair. Editorial Board of the Cochrane Review Group for Movement Disorders (1996-).

Carol Bower. International Clearinghouse for Birth Defects Surveillance and Research, Chair 2007-2009.

Glenys Dixon. Member of Autism Speaks International Autism Epidemiology Network Workgroup 2007-.

Jianghong Li. Associated Editor of Rural Sociology, published by the American Rural Sociological Society. (June 2005-).

Jianghong Li. Chief Guest Editor: A special issue on Social Determinants of Child Health and Wellbeing in Health Sociology Review June 2009.

Helen Leonard. Member of Autism Speaks International Autism Epidemiology Network Workgroup 2007- .

Helen Leonard. Member of Executive of RettSearch, International Consortium of Rett Syndrome Clinical Researchers 2009-.

Elizabeth Milne. Member of Management Committee of the Childhood Leukaemia International Consortium 2006-.

Melissa O'Donnell. Member of the International Society for the Prevention of Child Abuse and Neglect (ISPCAN).

Melissa O'Donnell. Member of the ISPCAN child maltreatment data working group 2008.

Adeleh Shirangi. International Commission on Occupational Health- Member of Scientific Committee on Reproductive Hazards.

Roz Walker. Perinatal Society of Australia and New Zealand (PSANZ) 2009.

Stephene Zubrick and Mitrou, FM. Workshop presentation. The Western Australian Aboriginal Child Health Survey: Research findings and policy recommendations. Aboriginal Policy Research Conference, Northern Affairs Canada, Strategic Research and Analysis

Directorate, Ottawa, Canada 13 March 2009.

National

Eve Blair. Australian Cerebral Palsy Register Policy Group, CP Institute (2008-).

Eve Blair. National Committee for Australasian Academy of Cerebral Palsy and Developmental Medicine, with responsibility for Newsletter (2006-).

Eve Blair. Scientific Advisory Committee for 3rd International CP Meeting, Sydney, Feb 2009 (2006-09).

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-.

Sue Byrne. The Australian Child and Adolescent Obesity Research Network.

Sue Byrne. ACAORN Longitudinal Studies Special Interest Group (co-chair).

Sue Byrne. The Eating Disorder Research Society.

Noula Gibson. Australian Physiotherapy Association National Paediatric Group, Chair (2008- ongoing).

E Glasson. Steering Committee - Development of a proposal for a National Autism Register, June 2009.

Tanyana Jackiewicz. National Community and Child Health Council.

Jocelyn Jones. Child Death Review Committee.

Cheryl Kickett-Tucker. Member Future Generations Network, Australian Alliance for Research in Children and Youth 2004-.

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-.

Sarah Love. Australian Cerebral Palsy Register Policy Group, CP Institute (2008-).

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.

Anne McKenzie. Consumer Observer, National Health and Medical Research Council.

Anne McKenzie. Senior Consumer Representative Consumer Health Forum of Australia (CHF), Canberra.

Anne McKenzie. Consumers Health Forum Consumer Representatives Selection Steering Committee.

Anne McKenzie. Consumer Representative, National Prescribing Service New Drugs Working Group Chair Editorial Group for Medicines Update.

Anne McKenzie. Consumer Representative CHF, Medicines Australia - Code of Conduct Committee.

Nick de Klerk. Australian NHMRC Asbestos Working Party, 2003-.

Nick de Klerk. Australian Working Group developing Radiation Protection Standard

for Exposure to ELF, 2003-.

Therese O'Sullivan. WA Executive for the Dietitians Association of Australia, Member 2009.

Kate Taylor. Councillor, Australian Research Alliance for Children and Youth (ARACY) (2009 - current).

Kate Taylor. Western Australia, Northern Territory and South Australia (WANTSAs) Research Collaboration. (December, 2009), University of Adelaide, Adelaide, South Australia.

Roz Walker. Member, Australian Research Alliance for Children & Youth.

Roz Walker. Member, Leaders in Indigenous Medical Education.

Stephen Zubrick. New Investigator Network: Building our research capacity for prevention. Australian Research Alliance for Children and Youth Conference 2009: Making Prevention Work. Melbourne Convention Centre, 2-4 September 2009.

Stephen Zubrick. Developmental pathways in language emergence from two to seven: Late starts and surprising arrivals Australian Institute for Family Studies Seminar Series, Melbourne, 8 October 2009.

Stephen Zubrick. Longitudinal scale performance: Quality characteristics of ordinal measures. Maximising the Value of Longitudinal Studies for Policy and Science: Methodological and Analysis Issues, Canberra, 12-13 November 2009.

Local

Eve Blair. Shaken Baby Syndrome Steering Committee, initiated by the WA Child Protection Council (2001-).

Eve Blair. Scientific Advisory Sub-committee to the Princess Margaret Hospital for Children Ethics Committee (2007-).

Jenny Bourke. Committee member, Board of Management, Parents of Children with Disabilities (Inc).

Carol Bower. WA Perinatal and Infant Mortality Committee Member 1993-.

Carol Bower. Scientific Sub-Committee of the Human Research Ethics Committee, Curtin University of Technology 2000-.

Carol Bower. Prenatal Diagnosis Committee, Department of Health WA, 2001-.

Sue Byrne. The Healthway Health Research Sub-Committee.

Sue Byrne. The UWA Vice Chancellor's Postdoctoral Fellowship Committee.

Heather D'Antoine. WA FASD Model of Care Working Group of the WA Child and Youth Health Network, Department of Health, WA.

Nick de Klerk. Clinical Drug Trial Committee, Sir Charles Gairdner Hospital, 1986-88, 1990-.

Nick de Klerk. Mesothelioma Committee of Western Australia - co-ordinating the Western Australian Mesothelioma Register, 1989-

Nick de Klerk. Busselton Population Medical Research Foundation, Board, 1997-.

Nick de Klerk. Busselton Population Medical Research Foundation, Scientific Committee, 1998-.

Nick de Klerk. Western Australian Air Quality Co-ordinating Committee Health Issues Group, 1998-.

Nick de Klerk. Western Australian Medical Radiation and Cancer Working Party, 2004-.

Francine Eades. WA Aboriginal Health & Information Ethics Committee, ongoing.

Francine Eades. Expert Advisory Committee (DoHA) – Development of the new.

National antenatal care guidelines, ongoing.

Francine Eades. WA Immunisation Alliance, ongoing.

Francine Eades. WA Immunisation Strategic Advisory Group, ongoing.

Francine Eades. WA Indigenous Sexual Health Advisory Committee, ongoing.

Francine Eades. Reference Group Member – “Management of coronary heart disease in the Indigenous population in WA – from Information to Action, ongoing.

Francine Eades. Metropolitan Sexual Health Advisory Committee (MSHAG), ongoing.

Francine Eades. WA Cancer Council Indigenous Advisory Committee, ongoing.

Francine Eades. WA Viral Hepatitis Advisory Committee, ongoing.

Francine Eades. Foetal Alcohol Spectrum Disorder Action Group, ongoing.

Francine Eades. Maternity Reference Group - Improving Maternity Services in WA, ongoing.

Francine Eades. WA Indigenous Primary Health Care Advisory Committee, past member.

Jocelyn Jones. Child Death Review 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 –.

David Lawrence. HealthRight Reference

Group.

Deborah Lehmann. Perinatal and Infant Mortality Committee, Ministry for Health, WA, 2005-.

Deborah Lehmann. Princess Margaret Hospital for Children Ethics Committee 2005-2009.

Deborah Lehmann. Meningitis Centre Committee 1998-.

Helen Leonard. Women's and Newborns' Health Network Executive Advisory Group.

Helen Leonard. Executive Committee Perth Epidemiology Group 2008-.

Josie Maxted. Women's Refuge Committee within the metropolitan area, ongoing.

Josie Maxted. Indigenous Social Work committee, ongoing.

Josie Maxted. Board member of Health Consumer Council, ongoing.

Josie Maxted. Member of AASW Aboriginal Social Work sub-committee, ongoing.

Josie Maxted. Vice Chair for Yorgum Aboriginal Counselling Service, ongoing.

Anne McKenzie. Chairperson, Health Consumers' Council WA Inc.

Anne McKenzie. Member, Health Consumers Council WA Inc.

Anne McKenzie. Consumer Representative, WA Child & Youth Health Network.

Anne McKenzie. Chair, Consumer and

Community Reference Group, WA Birth Defects Registry.

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 Alliance.

Anne McKenzie. Consumer Representative, Western Australian Audit of Surgical Mortality. Royal Australian College of Surgeons.

Anne McKenzie. Lay Member, Silver Chain Ethics Committee.

Elizabeth Milne. Research Committee of Cancer Council of WA (2005-9).

Hannah Moore. The Meningitis Centre Management Committee 2008-.

Raewyn Mutch. WA FASD Model of Care Working Group of the WA Child and Youth Health Network, Department of Health, WA.

Wendy Oddy. Executive Committee Member, International Society for Research into Human Milk and Lactation, 2008-2010.

Wendy Oddy. BFHI Advisory Group, Women and Newborn Network, WA, 2008-2010.

Wendy Oddy. Ngala WA Professional Development Advisory Group, 2008-2010.

Wendy Oddy. Infant and Early Child

Nutrition Working Group, HDWA, 2007-2010.

Wendy Oddy. Baby Friendly Hospital Initiative Assessor, Qualified March 2004; assessed King Edward Memorial Hospital June 2007 in a team of 3 assessors, assessing Kalgoorlie in Dec 2007. Assessed Joondalup in a team of 3 assessors July 2009.

Wendy Oddy. Chairperson, Breastfeeding Public Health Promotion campaign, North Metropolitan Health Service, Western Australia, 2005-present.

Colleen O'Leary. WA FASD Model of Care Working Group of the WA Child and Youth Health Network, Department of Health, WA.

Therese O'Sullivan. Louisa Alessandri Memorial Fund, Secretary 2009.

Glenn Pearson. Health Consumers Council (WA). 2007, elected member.

Glenn Pearson. Telethon Institute for Child Health Research Consumer and Community Advisory Council.

Monique Robinson. Chairperson of Telethon Institute for Child Health Research Postgraduate Student Society (IPoGS).

Monique Robinson. Committee member of the Dr Louisa Alessandri Memorial Fund.

Monique Robinson. Volunteer facilitator, Weight Management Group at Robin Winkler Clinic.

Monique Robinson. Australian

Psychological Society (APS)- Student Member.

Monique Robinson. Australian College of Clinical Psychologists- Student Member.

Monique Robinson. Australian Research Alliance for Children and Youth (ARACY)- Individual Member.

Monique Robinson. Developmental Origins of Health and Disease (DOHaD) Society- Student Member.

Monique Robinson. International Society for the Study of Behavioural Development- Student Member.

Monique Robinson. The University of Western Australia Sport and Recreation Association- Member.

Monique Robinson. Alumni Panel Member for Murdoch University School of Psychology Quinquennial Review.

Monique Robinson. Student Panel Member for UWA Australian University Quality Audit.

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. Member, Aboriginal Collaboration Council for Applied Research and Evaluation. Telethon Institute for Child Health Research (2008-).

Invited Presentations

Gina Ambrosini, Oddy WH. 3rd International Congress on Pre-diabetes and the Metabolic Syndrome, Dietary patterns and metabolic syndrome, April 2009, Nice, France. Two posters presented.

Gina Ambrosini, Oddy WH. 'Dietary patterns and the metabolic syndrome in an adolescent cohort' February 2009, MRC Nutrition Research Unit Cambridge, UK. Invited oral presentation.

Eve Blair. Causal pathways to cerebral palsy with local examples. Neuroepidemiology Research Group meeting, Perth, Feb 2009.

Eve Blair. Causal pathways to cerebral palsy. Keynote address. 3rd International Cerebral Palsy Conference, Sydney, Feb 2009.

Eve Blair. How to ensure validity of trends and comparisons of rates in CP. World Congress of CP Surveillance Systems. 3rd International Cerebral Palsy Conference, Sydney, Feb 2009.

Eve Blair. Overview of challenges concerning differential classification of cerebral palsy. World Congress of CP Surveillance Systems. 3rd International Cerebral Palsy Conference, Sydney, Feb 2009.

Eve Blair. Causal Pathways: association, causation and prevention. Population Sciences Divisional Seminar. June 2009.

Carol Bower. Fertility Society of Australia Annual Meeting, Perth 2009. Abnormalities after IVF.

Carol Bower. Australasian Health and Research Data Managers Association 18th Annual Scientific meeting, Perth 2009. Birth defects: the role of registers.

Carol Bower. Australian Birth Defects Society Annual Meeting, Sydney 2009. New perspectives on old problems – alcohol.

Carol Bower. Australian Birth Defects Society Annual Meeting, Sydney 2009. Folic acid and the prevention of neural tube defects – what have we achieved in 18 years?

Carol Bower. European Symposium on the Prevention of Congenital Anomalies, Bilbao 2009. Folic acid and the prevention of neural tube defects – what have we achieved in 18 years?

Carol Bower. Eurocat 24th Registry Leaders' Meeting, Bilbao 2009. Western Australian Birth Defects Registry and Stakeholder Consultation.

Carol Bower. Royal College of Obstetrics, Belfast, 2009. Western Australian Birth

Defects Registry - consumer involvement and statutory notification.

Lyn Colvin. Coordinator, Symposium and Workshop, 25th International Conference for Pharmaco-epidemiology and Therapeutic Risk Management, Providence, Rhode Island, USA, August 2009. Evaluating study designs for the measurement of drug exposure in pregnancy and Assessment of prenatal exposure to medications.

Nick de Klerk. Secular changes in outcomes after pre-term birth in Western Australia (and Session Chair). Exploiting Existing Data For Health Research, St Andrews, 2009.

Nick de Klerk. Sample Size Requirements in Medical Research. Perth Epidemiology Group, 2009.

Nick de Klerk. CRC for Spatial Information Health Workshop, Canberra, 2009.

Nick de Klerk. Epidemiology and community consequences of asbestos exposure in WA.

Nick deKlerk. National Centre for Asbestos Related Diseases, Annual Scientific Meeting, Sydney, 2009.

Nick de Klerk. Some issues in statistical analysis of micro-array data. Australian Medical Bioinformatics Resource (AMBeR), Annual Scientific Meeting, Brisbane, 2009.

Nick de Klerk. Introduction and overview – Child Health. Australasian Epidemiological Association Annual Scientific Meeting, Dunedin, New Zealand, 2009.

Nick de Klerk. Risk of mesothelioma in subjects with no known exposure to asbestos. 6th Perth Mesothelioma Centre Symposium, Perth, 2009.

Noula Gibson. The Australian Spasticity Assessment Scale and the Australian Cerebral Palsy Register CP Description Form. Kimberley Allied Health Conference, March 2009.

Noula Gibson. Hip surveillance in cerebral palsy. Kimberley Allied Health Conference, March 2009.

Noula Gibson. Strength training in children with and without cerebral palsy. Kimberley Allied Health Conference, March 2009.

Deborah Lehmann. The Kalgoorlie Otitis Media Research Project: microbiology of upper respiratory carriage with specific reference to Streptococcus pneumoniae The Australian Society for Microbiology Annual Scientific Meeting; 2009 Jul 6-10; Perth WA; 2009. p. 76.

Deborah Lehmann. The Kalgoorlie Otitis Media Research Project. Invited presentation. Audiological Society of Australia (WA Branch) State Conference; 2009 Nov 20; Perth WA; 2009.

Jenny Downs. Clinical guidelines for scoliosis and related projects; 3rd RettSearch Consortium Meeting; Chicago; United States; July 2009.

Jenny Downs. Measurement of functional abilities in Rett syndrome – using video to document skills; 3rd RettSearch Consortium Meeting; Chicago; United States; July 2009.

Helen Leonard. The pathway from childhood to adulthood for young people with an intellectual disability now and into the future: some statistics and some stories; A.S.S.I.D. (W.A.) State Conference What does the future hold for people with intellectual disability; Perth. September 2009.

Helen Leonard. Using epidemiology to piece together the jigsaw of Rett syndrome: insights from AussieRett and InterRett; 1st European Congress on Rett Syndrome; Milan; Italy. June 2009.

Helen Leonard. How can we be successful and make a difference in international collaborative clinical research; RettSearch Meeting; Chicago. July 2009.

Melissa O'Donnell. "Increasing Prevalence of Neonatal Withdrawal Syndrome: Population study of Maternal Factors and Child Protection Involvement." King Edward Memorial Hospital Scientific Seminar, Perth, June 2009.

Wendy Oddy. Rotary Club of Perth, WA. "Diet and mental health" December 2009.

Therese O'Sullivan, Oddy WH. 3rd International Congress on Pre-diabetes and the Metabolic Syndrome Fatty acids and metabolic syndrome, Glycemic intake and metabolic syndrome, April 2009, Nice, France. Two posters presented.

Anne McKenzie. Consumer panel member, National Intensive Care Conference, Perth. Oct 2009.

Anne McKenzie. Implementing as organisational strategy for greater

consumer and community participation. The School of Public Health Sheffield University. Sheffield UK. Nov 2009.

Anne McKenzie. Implementing as organisational strategy for greater consumer and community participation. Swansea University, Wales UK. Nov 2009.

Anne McKenzie. Consumer and community participation in research on medication safety in seniors. Exeter University. Devon UK Nov 2009.

Anne McKenzie. Training Workshops for Researchers. INVOLVE Support Unit. Eastleigh UK. Nov 2009.

Hannah Moore. Data linkage in respiratory disease research. National Centre for Immunisation Research and Surveillance (NCIRS) Special Meeting, Sydney, April 2009.

Colleen O'Leary. Murdoch Children's Research Institute, Melbourne, July 2009: The relationship between dose, pattern, and timing of prenatal alcohol exposure and fetal effects.

Colleen O'Leary. Complex Care Midwifery Study Day, York WA, August 2009: Maternal Alcohol Use/Abuse: Developing policies to prevent alcohol-related harms in women and their children.

Colleen O'Leary. Injury Control Council of WA conference, 'Strengthening Rural & Remote Communities' Community Safety and Injury Prevention Conference, Geraldton June 2009: Maternal alcohol use/abuse; using the evidence to inform policy and practice.

Colleen O'Leary. Faculty of Medicine, University of Manitoba, Canada, March 2009. Alcohol and pregnancy policy and research in Australia: Past, present, and future.

Colleen O'Leary. Curtin University Post-Graduate Child and Community Health Nursing Students, February and June 2009: Alcohol in Australia: Impact on Children and Families.

Therese O'Sullivan, Beilin LJ, Oddy WH. European Society of Hypertension, Fatty acids, blood pressure and the metabolic syndrome, June 2009, Milan, Italy. Presentation by Professor Beilin.

Therese O'Sullivan, Oddy WH. 'Fatty acid intake in Australian adolescents' presented at the Dietitians Association of Australia National Conference, Darwin May 2009. Highly commended in the 'Best of the Best' Category.

Therese O'Sullivan, Oddy WH. 'Fatty acid intake and high blood pressure in adolescents' presented at the National Heart Foundation Conference, Brisbane May 2009.

Therese O'Sullivan, Oddy WH. 'Carbohydrates – friend or foe?' presented as a Scientific Forum at the Telethon Institute for Child Health Research, September 2009.

Therese O'Sullivan, Oddy WH. 'Dietary fatty acid intake and blood pressure in Raine adolescents' presented as a Divisional Seminar at the Telethon Institute for Child Health Research, Nov 2009.

Monique Robinson. Developmental Origins of Health and Disease (DOHaD) International Conference (Santiago, Chile): 19th-22nd November 2009 "Low-moderate prenatal alcohol exposure and risk to child behavioural development"[poster]; "Hypertensive diseases of pregnancy and difficult babies: A large-scale cohort study"[poster]; "Prenatal stress events and behavioural development from age two to 14 years: The influence of the number, type and timing of stressful life experiences" [poster].

Monique Robinson. Society for Pediatric and Perinatal Epidemiologic Research (SPER) Annual Meeting (Anaheim, USA): 22nd-23rd June 2009 "Low-moderate prenatal alcohol exposure and risk to child behavioural development"[oral]; "Smoking cessation in pregnancy reduces child behavioural problems: A longitudinal prospective cohort study"[poster]; "Hypertensive diseases of pregnancy and difficult babies: A large-scale cohort study"[poster].

Adeleh Shirangi. American Veterinary Medical Association Annual Convention. 11-14 July 2009, Seattle, USA. Occupational Hazards in Veterinary Practice.

Adeleh Shirangi. American Veterinary Medical Association Annual Convention. 11-14 July 2009, Seattle, USA. Occupational Health Risks for Veterinarians: Anxiety, Depression, and Stress.

Adeleh Shirangi. American Veterinary Medical Association Annual Convention.

11-14 July 2009, Seattle, USA. Occupational Health Risks for Veterinarians: Reproduction 1.

Adeleh Shirangi. American Veterinary Medical Association Annual Convention. 11-14 July 2009, Seattle, USA. Occupational Health Risks for Veterinarians: Reproduction 2.

Adeleh Shirangi. Imperial College of London. 2008 March 11. Occupational Hazards in Veterinary Practice and Possible Effects on Reproductive Outcomes in Female Veterinarians

Adeleh Shirangi. Imperial College of London, 24th March 2009 - postgraduate MPH and MSc students. Introduction to Reproductive Epidemiology.

Katie Suriano, Curran J, Byrne SM, Davis EA. (2009). Sedentary behaviour is associated with increased metabolic risk in young children. Lawson Wilkins Pediatric Endocrine Society / European Society for Pediatric Endocrinology 8th Joint Meeting, New York City, USA.

Anke van Eekelen. Stress, brain maturation and disease vulnerability. Alzheimer Association WA, Perth, 23 July 2009.

Anke van Eekelen. Adolescent brain maturation: for better or worse? 31st annual scientific ANTA conference, Keynote lecture, Perth, 27 Aug 2009.

Anke van Eekelen. Stress, brain maturation & disease vulnerability. Burn Injury Research Unit, UWA, Perth, 14 Sept 2009.

Roz Walker. Engaging Indigenous Families

in Preparing Children for School.

Roz Walker & Pat Dudgeon. Catalyst Speakers, Samson and Delilah: Invisible Discourses Day 2 Session 4: National Roundtable on Research on Racism Towards Indigenous Australians, The Boat Shed, The University of Western Australia. 01 - 02 June 2009.

Roz Walker. Catalyst Speaker, Impacts of Racism, Day 1 Session 4: National Roundtable on Research on Racism Towards Indigenous Australians, The Boat Shed, The University of Western Australia. 01 - 02 June 2009.

Roz Walker, Deborah Harcourt, & Sharon Bessell. Involving Children and Young People in Research - Why do it? And what are the challenges? National Access Grid University of Western Australia hosted by the ARACY Research Network Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Parkville Vic. Perth, WA, 22 October, 2009. 1.00pm WST.

Roz Walker and Pat Dudgeon. Aboriginal Women's Health and Social and Emotional Wellbeing Child, Adolescent and Family Psychology Gathering, Australian Psychological Society, Fremantle Arts Centre, Fremantle October 15 2009.

Roz Walker, Fiona Stanley, E Stringer, E., S Soames, S., & Warburton Community Women. 'Not Just a Breakfast Program' – Celebrating the Breakfast Program, ARACY Seed Grant Seminar hosted by Professor Fiona Stanley, 15 July 2009.

Roz Walker. Engaging with Youth – Building Community Capital in Hedland. Guest Speaker, Celebration Dinner of the Hedland Youth Council, Hedland, WA. 8 May 2009.

Roz Walker. Engaging Indigenous Families in Preparing Children for School, the West Pilbara Seminar Series, the Early Years: Linking Theory to Practice. Lotteries House Karratha. WA.

Roz Walker & Sue Ferguson-Hill. Implementing the AEDI and I-AEDI in the Pilbara. WA Community Health Service, Lottery House, Karratha

Publications

2009 Institute Publications – 204

1. Ali M, Zhang G, Thomas WR, McLean CJ, Bizzantino JA, Laing IA, Martin AC, Goldblatt J, Le Souef PN, Hayden CM. Investigations into the role of ST2 in acute asthma in children. *Tissue Antigens* 2009;73(3):206-12.
2. Allen KL, Byrne SM, Forbes D, Oddy WH. Risk factors for full- and partial-syndrome early adolescent eating disorders: a population-based pregnancy cohort study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2009;48(8):800-09.
3. Ambrosini GL, de Klerk NH, O'Sullivan TA, Beilin LJ, Oddy WH. The reliability of a food frequency questionnaire for use among adolescents. *European Journal of Clinical Nutrition* 2009;63(10):1251-59.
4. Ambrosini GL, Oddy WH, Robinson M, O'Sullivan TA, Hands BP, de Klerk NH, Silburn SR, Zubrick SR, Kendall GE, Stanley FJ, Beilin LJ. Adolescent dietary patterns are associated with lifestyle and family psychosocial factors. *Public Health Nutrition* 2009;12(10):1807-15.
5. Angelicheva D, Tournev I, Guergueltcheva V, Mihaylova V, Azmanov DN, Morar B, Radionova M, Smith SJ, Zlatareva D, Stevens JM, Kaneva R, Bojinova V, Carter K, Brown M, Jablensky A, Kalaydjieva L, Sander JW. Partial epilepsy syndrome in a Gypsy family linked to 5q31.3-q32. *Epilepsia* 2009;50(7):1679-88.
6. Ansell TK, McFawn PK, Noble PB, West AR, Fernandes L, Mitchell HW. Potent bronchodilation and reduced stiffness by relaxant stimuli under dynamic conditions. *European Respiratory Journal* 2009;33(4):844-51.
7. Ansell TK, Noble PB, Mitchell HW, West AR, Fernandes LB, McFawn PK. Effects of simulated tidal and deep breathing on immature airway contraction to acetylcholine and nerve stimulation. *Respirology* 2009;14(7):991-98.
8. Banerjee B, Kicic A, Musk M, Sutanto EN, Stick SM, Chambers DC. Successful establishment of primary small airway cell cultures in human lung transplantation. *Respiratory Research* 2009;10:99.
9. Beesley AH, Firth MJ, Ford J, Weller RE, Freitas JR, Perera KU, Kees UR. Glucocorticoid resistance in T-lineage acute lymphoblastic leukaemia is associated with a proliferative metabolism. *British Journal of Cancer* 2009;100(12):1926-36.
10. Beesley AH, Weller RE, Senanayake S, Welch M, Kees UR. Receptor mutation is not a common mechanism of naturally occurring glucocorticoid resistance in leukaemia cell lines. *Leukemia Research* 2009;33(2):321-25.
11. Ben Zeev B, Bebbington A, Ho G, Leonard H, de Klerk N, Gak E, Vecksler M, Christodoulou J. The common BDNF polymorphism may be a modifier of disease severity in Rett syndrome. *Neurology* 2009;72(14):1242-47.
12. Bertram CM, Misso NL, Fogel-Petrovic M, Figueroa CD, Foster PS, Thompson PJ, Bhoola KD. Expression of kinin receptors on eosinophils: comparison of asthmatic patients and healthy subjects. *Journal of Leukocyte Biology* 2009;85(3):544-52.
13. Bessarab D, Solonec C, Gibbs T, Lehmann D, Wright M, (Editors). Not Just Scholars but Leaders: Learning Circles in Indigenous Health Research. An Indigenous Capacity Building Grant Community Report. Perth: Telethon Institute for Child Health Research, Curtin University of Technology, University of Western Australia and Combined Universities Centre for Rural Health; 2009.
14. Bishop DVM, Whitehouse AJO. The communication checklist - Self report (CC-SR) manual. London: Pearson, PsychCorp; 2009.
15. Bizzantino JA, Khoo SK, Zhang G, Martin AC, Rueter K, Geelhoed GC, Goldblatt J, Laing IA, Le Souef PN, Hayden CM. Leukotriene pathway polymorphisms are associated with altered cysteinyl leukotriene production in children with acute asthma. *Prostaglandins Leukotrienes and Essential Fatty Acids* 2009;81(1):9-15.
16. Blackwell JM, Fakiola M, Ibrahim ME, Jamieson SE, Jeronimo SB, Miller EN, Mishra A, Mohamed HS, Peacock CS, Raju M, Sundar S, Wilson ME. Genetics and visceral leishmaniasis: of mice and man. *Parasite Immunology* 2009;31(5):254-66.
17. Blackwell JM, Jamieson SE, Burgner D. HLA and infectious diseases. *Clinical Microbiology Reviews* 2009;22(2):370-85.
18. Blair E, Stanley F. The epidemiology of the cerebral palsies. In: Levene MI, Cherenak FA, Whittle M, editors. *Fetal and neonatal neurology and neurosurgery: fourth edition*. Edinburgh: Churchill Livingstone; 2009. p. 791-98.
19. Bosco A, McKenna KL, Firth MJ, Sly PD, Holt PG. A network modeling approach to analysis of the Th2 memory responses underlying human atopic disease. *Journal of Immunology* 2009;182(10):6011-21.
20. Bower C, D'Antoine H, Stanley FJ. Neural Tube Defects in Australia: Trends in Encephaloceles and Other Neural Tube Defects Before and After Promotion of Folic Acid Supplementation and Voluntary Food Fortification. *Birth Defects Research Part a-Clinical and Molecular Teratology* 2009;85(4):269-73.
21. Bower C, Rudy E, Callaghan A, Quick J, Cosgrove P. Report of the Birth Defects Registry of Western Australia 1980-2007. Perth: King Edward Hospital; 2009: 15.
22. Brennan S, Sly PD, Gangell CL, Sturges N, Winfield K, Wikstrom M, Gard S, Upham JW, on behalf of AREST CF. Alveolar macrophages and CC chemokines are increased in children with cystic fibrosis. *European Respiratory Journal* 2009;34(3):655-61.
23. Brinkman S, Sayers M, Goldfeld S, Kline J. Population monitoring of language and cognitive development in Australia: The Australian Early Development Index. *International Journal of Speech-Language Pathology* 2009;11(5):419-30.
24. Burchell JT, Wikstrom ME, Stumbles PA,

- Sly PD, Turner DJ. Attenuation of allergen-induced airway hyperresponsiveness is mediated by airway regulatory T cells. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 2009;296(3):L307-19.
25. Cadosch D, Sutanto M, Chan E, Mhawi A, Gautschi OP, von Katterfeld B, Filgueira L. Titanium uptake, induction of RANK-L expression and enhanced proliferation of human T-lymphocytes. *Journal of Orthopaedic Research* 2009.
26. Calogero C, Kusel MM, Van Bever HP, Sly PD. Management of childhood asthma in Western Australia. *Journal of Paediatrics and Child Health* 2009;45(3):139-48.
27. Calvert N, Damiani S, Sunario J, Bower C, Dickinson JE. The outcomes of pregnancies following a prenatal diagnosis of fetal exomphalos in Western Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2009;49(4):371-75.
28. Cannizzaro V, Berry LJ, Nicholls PK, Zosky GR, Turner DJ, Hantos Z, Sly PD. Lung volume recruitment maneuvers and respiratory system mechanics in mechanically ventilated mice. *Respiratory Physiology and Neurobiology* 2009;169(3):243-51.
29. Cannizzaro V, Berry LJ, Zosky GR, Turner DJ, Hantos Z, Sly PD. Impact of supplemental oxygen in mechanically ventilated adult and infant mice. *Respiratory Physiology and Neurobiology* 2009;165(1):61-66.
30. Carson C, Antoniou M, Christodoulou V, Messaritakis I, Quinnell RJ, Blackwell JM, Courtenay O. Selection of appropriate serological tests to measure the incidence of natural *Leishmania infantum* infection during DNA/MVA prime/boost canine vaccine trials. *Veterinary Parasitology* 2009;162(3-4):207-13.
31. Carson C, Antoniou M, Ruiz-Arguello MB, Alcamí A, Christodoulou V, Messaritakis I, Blackwell JM, Courtenay O. A prime/boost DNA/Modified vaccinia virus Ankara vaccine expressing recombinant *Leishmania* DNA encoding TRYP is safe and immunogenic in outbred dogs, the reservoir of zoonotic visceral leishmaniasis. *Vaccine* 2009;27(7):1080-6.
32. Clarke W, Jones T, Rewers A, Dunger D, Klingensmith GJ. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatric Diabetes* 2009;10 Suppl 12:134-45.
33. Colvin L, Bower C. A retrospective population-based study of childhood hospital admissions with record linkage to a birth defects registry. *BMC Pediatrics* 2009;9:32.
34. Colvin L, Slack-Smith L, Stanley FJ, Bower C. Pharmacovigilance in pregnancy using population-based linked datasets. *Pharmacoepidemiology and Drug Safety* 2009;18(3):211-25.
35. Cooper PR, McParland BE, Mitchell HW, Noble PB, Politi AZ, Rasmeyer AR, West AR. Airway mechanics and methods used to visualize smooth muscle dynamics in vitro. *Pulmonary Pharmacology and Therapeutics* 2009;22(5):398-406.
36. Cui J, de Klerk N, Abramson M, Del Monaco A, Benke G, Dennekamp M, Musk AW, Sim M. Fractional polynomials and model selection in generalized estimating equations analysis, with an application to a longitudinal epidemiologic study in Australia. *American Journal of Epidemiology* 2009;169(1):113-21.
37. Dawson S, Glasson EJ, Dixon G, Bower C. Birth defects in children with Autism spectrum Disorders: A population-based, nested case-control study. *American Journal of Epidemiology* 2009;169(11):1296-303.
38. De Souza E, Halliday J, Chan A, Bower C, Morris JK. Recurrence risks for trisomies 13, 18, and 21. *American Journal of Medical Genetics Part A* 2009;149A(12):2716-22.
39. Dixon G, Badawi N, French D, Kurinczuk JJ. Can parents accurately screen children at risk of developmental delay? *Journal of Paediatrics and Child Health* 2009;45(5):268-73.
40. Dockery A, Li J, Kendall G. Parents' work patterns and adolescent mental health. *Social Science and Medicine* 2009;68(4):689-98.
41. Douglas TA, Brennan S, Gard S, Berry L, Gangell C, Stick SM, Clements BS, Sly PD. Acquisition and eradication of *P. aeruginosa* in young children with cystic fibrosis. *European Respiratory Journal* 2009;33(2):305-11.
42. Dove ER, Byrne SM, Bruce NW. Effect of dichotomous thinking on the association of depression with BMI and weight change among obese females. *Behaviour Research and Therapy* 2009;47(6):529-34.
43. Downs J, Young D, de Klerk N, Bebbington A, Baikie G, Leonard H. Impact of Scoliosis Surgery on Activities of Daily Living in Females With Rett Syndrome. *Journal of Pediatric Orthopaedics* 2009;29(4):369-74.
44. Drew N, Adams Y, Walker R. Issues in mental health assessment with Indigenous Australians. In: Purdie N, Dudgeon P, Walker R, editors. *Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practices*. Canberra: Office of Aboriginal and Torres Strait Islander Health, Department of Health and Aging; 2009. p. 191-210.
45. Drews AC, Pizzichini MMM, Pizzichini E, Pereira MU, Pitrez PM, Jones MH, Sly PD, Stein RT. Neutrophilic airway inflammation is a main feature of induced sputum in nonatopic asthmatic children. *Allergy* 2009;64(11):1597-601.
46. Dudgeon P, Wright M, Paradies Y, Garvey D, Walker I. The social, cultural and historical context of Aboriginal and Torres Strait Islander Australians. In: Purdie N, Dudgeon P, Walker R, editors. *Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practices*. Canberra: Office of Aboriginal and Torres Strait Islander Health, Department of Health and Aging; 2009. p. 25-42.
47. Dyke P, Mulroy S, Leonard H. Siblings

- of children with disabilities: challenges and opportunities. *Acta Paediatrica* 2009;98(1):23-24.
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This Annual Report was produced by the Public Relations Office of the Telethon Institute for Child Health Research. Published in May 2010.

We wish to acknowledge the staff of the Telethon Institute for Child Health Research for their contributions to the 2009 Annual Report.