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TELETHON INSTITUTE FOR Child Health Research

PREVENTION
INNOVATION
DEDICATION

Contents

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.

Prevention…. is our aim. While more effective treatments are important, how much better it would be if we could stop diseases, disorders and disabilities in their tracks, before they emerge to damage the life of a child. Sounds like a dream? Not to us. These problems are caused by a complex interaction between genetics and environmental factors. If we can map the routes that lead to disease, we can identify early opportunities to stop it.

Innovation… is what happens when you bring together a critical mass of outstanding minds. The Institute's collaborative, cross-disciplinary approach is at the cutting edge of medical research.

Dedication… is what you get from the more than 400 people employed at the Telethon Institute who have committed themselves to improving the health and life chances of children, not just in Australia, but throughout the world. We know that it's important work and we're proud to be doing it.

Division of Cancer Biology

Overview

The Cancer Biology Division focuses primarily on SCL, a gene which is essential for normal blood cell maturation. Without SCL, mice die due to a fatal lack of blood cells. Addtionally, abnormally high amounts of SCL have been shown to be strongly correlated with T cell leukaemia in humans and in mice. Indeed, mice engineered to express high amounts of SCL in T cells eventually develop T cell leukaemia. We have now engineered mice which express high amounts of SCL in an inducible fashion to better understand the leukaemic process driven by SCL. We are also using cDNA libary (library of genes) screening to identify novel genes which cause T cell leukaemia.

SCL is also expressed in the developing brain. It is therefore proposed that expresion of SCL in the brain may play as crucial a role in brain development as in blood cell maturation. We are the first group in the world to engineer a mouse which has SCL function removed in early brain development. It is hoped that this brain SCL knockout mouse will provide new insights into how the brain develops.

T cell leukaemia and development of the central nervous system

The role of transcription factor SCL in T cell development

David Izon, Monique Smeets, Joachim Göthert

It is already known the SCL overexpression induces T cell leukaemia in mice and humans. However, the mechanism by which SCL deregulates normal T cell differentiation is still poorly understood. Consequently, we chose to generate an inducible SCL transgenic driven by the lck promoter to specifically overexpress SCL in developing T cells.

Analysis of T cell development of inducible SCL transgenic mice has demonstrated a significant deregulation of the normal T cell differentiative processes. Previous research had pointed to a specific sub-population of cells as being deregulated by SCL. However, our inducible SCL transgenic model has demonstrated that another distinct population is the target of SCL overexpression. Additionally, we have also discovered additional novel abnormalities in T cell development caused by SCL overexpression which help explain why T cell leukaemia develops. It is hoped that investigating the causes of T-cell leukaemia will provide a basis for more rational and specific treatment regimens for leukaemia.

SCL expression & function in the central nervous system

JAM van Eekelen

SCL is a transcription factor that is expressed in the central nervous system (CNS). The aim of this project is to further investigate the role of this gene in the mouse brain based on the underlying hypothesis that a highly regulated and highly specific expression of the SCL-gene in CNS implies an important yet undefined function for SCL in brain cells.

Detailed investigation into the cellular phenotype of mature SCL-expressing neurons in the superior colliculus (SC), where SCL expression is highly abundant, specifically in the dorsal visual layers of this tectal structure elucudated co-localisation of the *SCL-LacZ* reporter gene and GABA-immunoreactivity (ir) in the majority of neurons in the superficial grey layer (SGS) of SC of *SCL-LacZ* KI mice. Similarly, we have observed co-localisation of *LacZ* and transcription factor Pax7-ir in SGS of SC. To our surprise, colocalisation of Scl and Pax7 was only after birth. During embryogenesis, SCL and Pax7 were expressed in the same midbrain regions, but did not co-localise in the same cells. This is the first evidence of a change from developing to mature neurons and supports the view that the role of SCL in neurons after birth is essentially different from its earlier role during brain development.

Our previous results have shown that conditional ablation of SCL function during embryogenesis in neuronal-SCL deleted mice displayed a striking phenotype. Their survival rate after birth was severely affected, they were significantly growth retarded and displayed a hyperactive behaviour from pnw2 onwards. Moreover, lacZ staining had disappeared almost completely from hindbrain and was significantly reduced in caudal thalamus and midbrain. We have now quantified this reduction using the optical fractionator method. In ventral hindbrain, the reduction in SCL null/LacZ+ neurons was 95%, and the percentage of Scl null/LacZ+ neurons in SGS of SC was 30% reduced. Less intense LacZ staining in the mid-hindbrain was already apparent at E12.5, indicating that some SCL null neurons are not generated or lost early in brain development. We are currently investigating if functional compensation by Tal2, a homologous bHLH factor to SCL, explains the survival of the remaining SCL null/LacZ+ cells. We have also addressed the possibility that retinotectal projections to the SGS in SC were impaired affecting vision in neuronal SCL deleted mice. Although innervation of the SGS by retinal ganglion cells and the head turning reflex as a first indication of impaired vision were reduced, the mice did not appear to be completely blind.

Finally, we have studied the cohort of adult neuronal-SCL deleted mice, based on inter-crossed 0.9E3creER(T), Scl-LacZ KI and floxed SCL transgenics. Triple positive offspring and their control littermates were fed with a tamoxifen diet for 4 weeks starting at the age of weaning. We did not observe any of the phenotypic aspects seen in the embryonically SCL deleted mice. This overall outcome underlines a crucial role for SCL as a neurogenic factor in neuronal differentiation.

Staff and Students

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Theses passed

Cara Bradley Ph.D. University of Western Australia 2004. Cell fate determinant characterisitics of the transcription factor SCL in blood and brain.

External Committees

National

David Izon. NHMRC Development Grant Committee. 2004.

Division of Cell Biology

Overview

Research in the Division of Cell Biology focuses primarily on the mechanisms underlying susceptibility to inflammatory diseases in the respiratory tract, in particular those caused by allergy and/or infections. Work in the Division has been largely responsible for creation of what has become one of the cental paradigms of modern paediatric medicine, notably that risk for these and related diseases is determined primarily by developmental factors which control the transition of the immune system from the quiescent, which is characteristic of fetal life, to the fully functional status seen in "mature" individuals. The key to this transition is the unlocking of a variety of cytokine driven effector functions which are suppressed *in utero* in order to protect the placenta from inflammatory damage. These same mechanisms are necessary for resistance to both infections and allergy, and we have shown that the rate at which they mature functionally during the preschool years is a key determinant of risk for allergy, respiratory infection and asthma. Much of the work of the Division is targeted at more detailed definition of these mechanisms, with the aim of development of early intervention strategies in childhood to reduce disease susceptibility, ideally to prevent disease onset. The research effect is paralleled by a second stream involving the use of experimental animal models, where the target is control of cell populations in the airway wall which are responsible for triggering the "late phase response" in asthma. This part of the response is due to activation of T-lymphocytes in the airway mucosa, and is largely responsible for progression from acute to chronic asthma. Earlier work for the Division has identified the principal cellular trigger of this response, airway mucosal Dendritic Cells, and our ongoing studies are aimed at development of new therapeutic strategies to dampen their functions in asthmatics.

Human Studies - aetiology and pathogenesis of atopy and asthma

Immunoprophylaxis of asthma and atopy

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

We are in the late stages of developing a program under the auspices of the Immune Tolerance Network of the US National Institutes of Health, for a multicentre clinical trial on asthma/allergy prevention in high risk children. Preliminary approval has been granted by NIH and the US Food and Drug Administration, and final approval is expected by May 2005. The trial is based on the results of research in TICHR and in other centres in Europe and USA, indicating that the basis for natural resistance to sensitisation to inhalant allergens, and hence resistance to atopic asthma, is the development during early childhood of a form of immunological tolerance to inhaled allergen. This process is driven by repeated allergen exposure of the mucosal surfaces of the oropharynx, the nose, and the large airways, and the overall efficiency of tolerance induction is directly related to exposure intensity. In the trial we will seek to intensify the tolerance process in children at risk of allergy, by repeated exposure of the oral mucosa for a one year period, to a mixture of the three most important aeroallergens known to be associated with asthma (mite, cat and grass). The aim of the initial trial is to reduce atopy and asthma prevalence in these children over a 3 year follow-up period by 50%. An important component of the trial design involves detailed investigations on underlying allergen-specific immune responses in the children, throughout the entire study, to provide definitive information on underlying mechanisms.

An immunoepidemiological approach to asthma

J Rowe, T Heaton, E Hollams, S Yerkovich, D Suriyaarachchi, M Serralha, PD Sly and PG Holt in collaboration with S Turner, P Le Souef, Department of Paediatrics, the University of Western Australia and R Aalberse, Sanquin Laboratories, Amsterdam

This study is focusing upon the relationships between immune response parameters in children as measured in PBMC or serum, and clinical phenotypes related to asthma and allergy, in a birth cohort of 11 year olds. The principal aims are to identify immune response phenotypes, in relation to reactivity to inhalant allergens and/or global immune capacity, and susceptibility to development of various forms of atopy/asthma-related symptomatology. The principal findings to date, some of which have recently been published in *The Lancet* include (i) identification of an important co-factor role for Th1 immunity in driving disease severity, in particular airways hyperresponsiveness, (ii) the key role of IL-5 and eosinophils in asthma-related symptomatology in this age group, and (iii) the association between hyperproduction of IL-10 and airways hyperresponsiveness in non atopics. We hypothesise that the latter may compromise the initial phase of host defence against respiratory viral infections, thus increasing susceptibility to spread of infection to the small airways, precipitating wheeze in susceptible subjects. Ongoing analyses are currently focusing on relationships between exhaled NO and asthma phenotypes, and preliminary results suggest that NO may protect against eosinophil-driven airways inflammation amongst a subset of children. Additionally, genotyping of the cohort is in progress and analyses of relationships between genotypes and immune response phenotypes will be undertaken this year.

Eosinophil/basophil precursors in peripheral blood as a risk factor for viral induced wheeze during infancy

M Kusel, K Holt, B Holt, P D Sly, P G Holt in collaboration with S Johnston, Imperial College, London, and J Denburg, McMaster University, Hamilton, Canada

A hallmark of atopy is eosinophilic inflammation, accompanied by up-regulation, differentiation and recruitment of eosinophil/basophil (Eo/B) progenitors in marrow and tissues. Previous studies have shown that Eo/B progenitors are altered in cord blood (CB) in relation to atopic risk and development of atopy in infancy. In a recent study we have assessed CB progenitors in infants at high risk (HR) for atopy and asthma, in relation to the patterns of acute respiratory illness (ARI) expressed by the infants during their first year. We studied CB from a cohort of 39 HR infants by flow cytometry for CD34+ progenitor phenotype, and by Eo/B-colony forming unit (CFU) responses to cytokine stimulation. Progenitor frequencies and phenotypes were assessed in relation to ARI and accompanying symptomatology in the first year of life. A consistent relationship was observed between increased numbers of GM-CSF- and IL-3-responsive Eo/B-CFU at birth and the frequency/severity of ARI during early infancy. These included associations between GM-CSF and/or IL-3-CFU and ARI with wheeze or fever, and were mirrored by comparable associations between ARI and GM-CSFR+CD34+ cell numbers in CB. Moreover, the elevation in numbers of GM-CSFR+ and IL-3R+ CD34+ cells in ARI-prone subjects was accompanied by a reciprocal decrease in the proportion of IL-5R+ cells in CB, reflecting a less mature myeloid progenitor phenotype in these subjects.

The increased frequency of IL-3/GM-CSF-responsive Eo/B progenitors in HR infants provides a plausible mechanism for the generation of tissue eosinophilia at sites of airway ARI. This mechanism may underlie some of the known epidemiological associations between atopy and wheezing in response to viral ARIs amongst HR infants, and the subsequent development of atopic asthma.

Factors influencing the development of asthma and allergy in a high risk population

J Rowe, D Suriyaarachchi, M Serralha, L Subrata, CE Ladyman, A Sadowska and PG Holt in collaboration with M Kusel and PD Sly (Clinical Sciences, TICHR)

At birth, several aspects of immune function are immature, with adult levels of competency not being achieved for several years. Within the overall population, the rate at which maturation occurs is heterogeneous, and several reports have demonstrated this process to be slower in those at high genetic risk of atopy. Furthermore, environmental factors such as exposure to infectious agents, have also been demonstrated to influence the rate of immune maturation. As part of a collaborative project with Clinical Sciences in TICHR, we are prospectively studying immune function in cryopreserved peripheral blood mononuclear cell samples collected from a cohort of 263 children followed from birth until age 5 years. Clinical phenotypes related to atopy and asthma have been documented, together with the incidence of every infectious respiratory episode. To date, we have completed laboratory work based on all samples up to the end of age 2 years. Statistical analyses, are in progress to identify factors influencing the rate of immune maturation, and how this in turn, influences the development of atopy and asthma symptoms. This study is ongoing.

The W.A. Pregnancy Cohort 13 year old Asthma Study

E Hollams, CE Ladyman, A Sadowska, M Serralha, D Suriyaarachchi, BJ Holt and PG Holt in collaboration with PD Sly (Clinical Sciences, TICHR)

The W.A. Pregnancy Cohort was recruited in 1989 to investigate the effects of fetal monitoring on pregnancy outcome. In the 13 year follow-up of this study, we intend to investigate 1500 of these cohort members, with the aim of discriminating asthma and allergy phenotypes. The study will examine the clinical history, genetic profile, lung physiology and immunology of the participants. Immunological assays to be performed include allergen skin prick testing, eosinophil counts, and measurement of IgE and IgG, eosinophil cationic protein and soluble CD14 from plasma. In addition, we will investigate both allergen-specific T-cell immunity and global measures of immune competence. Cryopreserved peripheral blood mononuclear cells (PBMCs) will be cultured to establish cytokine expression in response to allergens (house dust mite and rye), polyclonal stimuli (PHA, PMA/Ionoymcin, and Staphylococcal Enterotoxin B) and innate immune stimuli (LPS, IFNγ + LPS, polyIC). Secreted IL-10, TNFα, IL-12 and IFNγ will be measured for the innate immunity stimuli and controls. IL-5, IL-10. IL-13 and IFNγ will be measured for the remaining stimuli and controls, while IL-4 receptor and IL-9 will be quantitated at the mRNA level. At the end of the study, the information collected will be integrated to identify biomarkers important for the discrimination of asthma subgroups, and we aim to develop algorithms using these biomarkers which will serve as aids in diagnosis, prognosis and treatment choice for asthma and allergy. By the end of 2004, blood had been collected and PBMCs cryopreserved from 636 subjects, and PBMC cultures had been performed from 450 subjects.

Identification of novel atopy-associated genes by microarray

A Bosco, K McKenna, C Devitt and PG Holt in collaboration with PD Sly (Clinical Sciences, TICHR)

Studies are in progress to identify novel genes distinguishing T-cell memory responses in atopics and nonatopics utilising Affymetrix microarray technology. This has involved kinetic studies of PBMC responses to house dust mite (HDM) allergen. The preferential expression of a panel of known Th2 index genes, such as IL-4, IL-5, IL-9 and IL-13 were identified in atopics after HDM stimulation, and are employed as positive internal controls in these analyses. Analysis of the microarray results to date by hierarchical clustering has identified two major atopy-associated gene clusters containing several novel genes that exhibited expression patterns similar to the Th2 index genes. The first cluster peaked early following HDM

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stimulation, and was enriched for genes involved in cell signalling. The second cluster peaked late and was enriched for genes associated with effector function. The preferential expression of these novel genes in atopics following HDM stimulation was confirmed by quantitative RT-PCR in at least two additional patient populations. Further validation studies are in progress employing siRNA. Future studies will focus on the role of various cell types ($CD4^+$ T-cells, $CD8^+$ T-cells and non T-cells) in the allergen-specific response, and the identification of genes associated with disease intensity.

Human Studies - innate immunity

Functional genomics of toll-like receptor (TLR)-4 in epithelial cell responses to respiratory syncytial virus (RSV)

MK Tulic, R Hurrelbrink, S Yerkovich, P McMinn and PG Holt

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections and is responsible for majority of hospitalisations of children during their first 2-3 years of life. Currently there is no vaccine against RSV. TLR4 is the receptor involved in bacterial (LPS)-induced signal transduction and recently it has been shown to recognise the F-protein of RSV. Genetic variations in hTLR4 are associated with interrupted LPS signalling. The primary target for RSV is the respiratory epithelium. We hypothesise that polymorphisms in TLR4 gene are associated with modified *in vitro* epithelial cell (EC) response to RSV and plan to identify key genetic variants involved in initiation of innate and adaptive immune responses to RSV in these cells. To date, we have successfully cloned and transfected wildtype TLR4 into a number of different EC lines, achieving >80% transfection efficiency. We have shown transfected kidney EC (HEK293) to favour IL-8 production at 24 hours after LPS or RSV exposure but TLR4 transfected human bronchial EC (HBE) to favour IL-6 compared to untransfected controls. Synergistic cytokine response is seen when both LPS and RSV are added together. Furthermore, we have identified and recently cloned two key TLR4 variants which we plan to use to transfect into epithelial cells and compare to responses already established with the TLR4 WT control. The long term aim of this study is to use the *in vitro* information in our *in vivo* epidemiological study where we will measure the RSV response in children with severe versus mild forms of the disease to assess whether these differences are linked to their frequency of viral infections and/or their genetic variation in TLR4. Therapies that target the expression of this gene may be useful in altering the course of viral infections in young children and ultimately reducing the subsequent risk of their development of allergic disease.

Maturation of the innate immune system proceeds unexpectedly slowly with age

S Yerkovich, D Suriyaarachchi, JW Upham and PG Holt

It is known that young children have greater susceptibility to infection due to generalised immaturity of their immune systems. The innate immune system provides the first line of defence against invading pathogens, and in particular provides signals which are obligatory for triggering the Th1 responses that are important for host defence. At birth and during early childhood the immune response displays the typical fetal pattern dominated by Th2 cytokine production and a low Th1 component. The aim of this study was to investigate the kinetics of postnatal development of the innate immune system by assessing the response to lipopolysaccharide (LPS) in terms of production of the Th1-associated cytokines IL-12, IL-18, IL-23, IFNγ and MxA (surrogate for type 1 interferon) and the inflammatory modulators IL-6, IL-10 and TNFα. For these studies we used mononuclear cells obtained from cord blood, children aged 1, 4 and 13 years and adults. There was a strikingly similar developmental pattern for all cytokines studied, with reduced responsiveness to stimulation at birth and in younger children, and adult levels not being approached until age 13 yrs. We also investigated expression of TLR4, the receptor for LPS, and found it showed the same developmental profile as did the cytokines. These results indicate that TLR4 expression may be a rate limiting mechanism determining Th1 cytokine response capacity during childhood.

Antigen presenting cells during infancy

A Rate, PG Holt and JW Upham

Dendritic cells (DC) are antigen presenting cells that are fundamental to regulation of the immune response. Our studies have focussed on the way in which DC function changes with age, and how this is related to the development and perpetuation of allergic diseases such as asthma. We have examined DC subsets at 6 and 12 months of age in a large cohort of children, and have shown that the relative proportions of myeloid and plasmacytoid DC subsets in peripheral blood are independent predictors of the risk of respiratory viral infections during the first year of life. Ongoing studies will involve following these children to the age of 5 years, and determining whether there is a relationship between DC subsets and the onset of allergic sensitisation and/or asthma. In a recently completed study, we have shown that the ability of cord blood monocytes to up-regulate expression of class II MHC in response to IFNγ is also closely associated with *in vitro* immune responses at birth, and to the risk of allergic disease at age 2 years.

Airway epithelial cells and regulation of dendritic cell function

A Rate and JW Upham

In a new collaboration with the Department of Respiratory Medicine at Princess Margaret Hospital, we have been studying the regulation of dendritic cell (DC) function by airway epithelial cells. DC are situated in close proximity to epithelial cells, and it is likely that epithelial cells have an important role in regulating the way that dendritic cells react to inhaled allergens. Airway brushings have been obtained from healthy children, and primary epithelial cell cultures established. These cells secrete soluble factors that inhibit cytokine production by allergen exposed DC. Identifying the nature of these factor(s), and whether these regulatory processes are also operative in children with asthma is the focus of ongoing studies.

Regulation of the allergic response by components of gram positive bacteria

R Taylor and JW Upham in collaboration with P Richmond (Department of Paediatrics, The University of Western Australia)

Various microbial components interact with toll-like receptors (TLRs), key molecules involved in innate and adaptive immunity. We are currently examining TLR2, the receptor that is mainly involved in recognising components of Gram-positive bacteria, and how this might regulate allergic inflammation. We have shown that components of the Gram-positive bacteria *Staph aureus* markedly inhibit the ability of allergen-stimulated peripheral blood mononuclear cells to produce the Th2 cytokines IL-5 and IL-13 in atopic individuals, but have no effect on responses in non-atopic individuals. The mechanisms responsible for these effects are currently being investigated.

Human Studies - paediatric vaccines

Vaccine-induced Th1 versus Th2 immunity: the balancing act

J Rowe, S Yerkovich, D Suriyaarachchi and PG Holt in collaboration with PD Sly (Clinical Sciences, TICHR), P Richmond (Department of Paediatrics, The University of Western Australia) R Loh, E Fisher and L Feddema (Department of Clinical Immunology, Princess Margaret Hospital for Children)

Early childhood represents a period of increased susceptibility to infectious disease, and as such, it is a priority to develop vaccines that can be safely introduced during these crucial first months of life, while still providing long term protection. The shift away from a whole cell diphtheria tetanus pertussis (DTP) vaccine to an acellular DTP vaccine is one illustration whereby safety has been improved without compromising efficacy. However, recent studies in older children receiving acellular DTP boosters reveal an increased incidence of redness and swelling at the vaccine site in those children exclusively vaccinated in infancy with the acellular version of the vaccine, although the mechanism underlying these local reactions are not understood. We have examined this issue in a cohort of 46 pre-school aged children, comparing immune response profiles of those primed in infancy with either the acellular or whole cell DTP vaccine. Our results suggest that vigorous Th2-polarised cellular immune responses to vaccine antigens in those primed with the acellular vaccine are associated with the increased incidence of local reactions. These results highlight the importance of achieving the optimal balance between vaccine-induced Th1 versus Th2 immunity, and emphasises the value of assessments of both humoral and cellular responses in the development of future vaccines.

Antigen presenting cell (APC) function as a determinant of vaccine responsiveness during infancy

JW Upham, A Rate, J Rowe and PG Holt in collaboration with M Kusel and PD Sly (Clinical Sciences, TICHR)

Recent studies in the Division have highlighted the importance of the role of cellular immunity in vaccine responsiveness in infants, and in particular have demonstrated that capacity to develop stable cellular immune memory to vaccines such as DTaP is highly variable within the paediatric population. It is also becoming evident that (i) cellular immunity in the form of cytokine production is central to host defence against pathogens, and operates in synergy with vaccine-induced antibody, and (ii) cellular immunity can also potentially contribute to vaccine side effects. The low frequency of T-memory cells in infant PBMC greatly complicates research in this important area, and there is an urgent need for more sensitive methodology to detect cellular immune memory in vaccinated infants. In a recent series of studies we have sought to improve vaccine-specific T-memory detection in PBMC cultures from infants by optimisation of APC function, which is known to be deficient in this age group. We have utilised cryobanked paired samples of PBMC collected at birth (cord blood) and subsequently at age 12 months from DTaP vaccinated infants, as follows. In a two step process, monocyte-derived dendritic cells (DC) were first "matured" from cord blood in the presence of GM-CSF and IL-4 over a one week period; PBMC cultures were then established from the matched (autologous) 12 month sample, and stimulated with antigens from the DTaP vaccine. A proportion of the latter cultures were supplemented with autologous "matured" DC, and this supplementation resulted in unmasking of cellular immune memory which was not demonstrable in the original PBMC cultures. These findings have important implications in a number of areas. They firstly demonstrate that priming of vaccine specific immunity and reactivation of T-memory cells are governed by subtly different mechanisms. Secondly, they imply that the key factors limiting the capacity of infant vaccines to stimulate protective cellular immunity may be operative within the innate immune system, rather than within the T-memory system itself.

Immune responses following Measles Mumps Rubella and Varicella vaccinations

S Yerkovich, J Rowe, D Suriyaarachchi, T Heaton, E Hollams, C Ladyman, M Serralha, A Sadowska and PG Holt in collaboration with P Richmond (Department of Paediatrics, The University of Western Australia), R Loh (Department of Clinical Immunology, Princess Margaret Hospital for Children) and PD Sly (Clinical Sciences, TICHR)

Previous studies from our laboratory have demonstrated a progressive increase in the Th1 component of immune function between the ages of 12 and 18 months. During this period Th1 competence rapidly rises from the low fetal levels seen at birth towards the higher levels seen in adults. We are seeking to identify environmental factors that drive this stage of immune maturation, and have examined the possibility that the measles mumps rubella (MMR) vaccine given at 12 months of age, which is a potent Th1 stimulus may be a contributing factor. We also investigated the effect of vaccinating with varicella at the same time as the

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MMR as there has been much debate about multiple vaccines and whether they "overload" the immune system. Therefore a cohort of 12 month old children was established with 3 groups in which one group had their MMR vaccination delayed by 6 weeks to assess the effect of vaccination, and separate groups that received MMR alone or in combination with varicella (MMR-V). The results demonstrated that neither the MMR nor the MMR-V vaccinations affected polyclonal Th1 or Th2 responses as compared to the unvaccinated group. Also there was no difference in the measles-specific immune response between the MMR and MMR-V vaccinated groups. This study showed that MMR vaccination alone or in combination with the varicella vaccine does not alter Th1 immune maturation. Furthermore, the varicella vaccine, given at the same time as the MMR vaccine does not alter the cellular response to individual vaccine components.

Animal Model Studies

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

DH Strickland, JA Thomas, PA Stumbles, PG Holt, in collaboration with GR Zosky, DJ Turner and PD Sly (Clinical Sciences, TICHR)

Currently, this group employs a rat model to investigate Allergic Airways Inflammation. Our earlier published studies describe the rapid maturation of AMDC, assessed as an up-regulation of co-stimulatory molecule CD86 expression, after a single aerosol challenge of pre-sensitised animals. This is mediated by cognate interactions with local $CD4^+$ Th cells, and in common with the human disease asthma, results in the development of airways hyper responsiveness (AHR). More recent studies have focused upon examining the effect of repeated aerosol exposure on AMDC- T cell interactions. Consecutive daily aerosol challenge (>3 days) blocks the capacity for reactivation of AMDC, as assessed by the return of the AMDC population to their constitutively quiescent state. Importantly, there is no ensuing development of AHR in response to rechallenge with OVA aerosol, despite the continued presence of the OVA-specific $CD4^+$ Th cells within the airway mucosa.

An *in vitro* model of this process has been developed and utilised to demonstrate that in the face of ongoing aeroallergen exposure, a population of $CD4^+CD25^+CTLA4^+Foxp3^+$ regulatory T cells (Tr) develops within large airways tissue, which inhibit Th cell mediated up-regulation of CD86 on AMDC. The maintenance of protective Tr activity is dependent upon continuing allergen stimulation, as cessation of allergen exposure leads to waning of Tr function, release of AMDC from control and resurgence of AHR. Ongoing studies are focusing upon the mechanism(s) associated with Tr cell regulation of AMDC within the large airways. In related ongoing studies, utilising different rat strains, we are investigating the possibility of a level of genetic regulation of this Tr cell mediated activity.

Antigen sampling and transport by airway mucosal dendritic cells (AMDC) is accelerated following inhalation of a bacterial stimulus

DH Strickland, FL Jahnsen, JA Thomas, IT Tobagus, S Napoli, PA Stumbles, PG Holt in collaboration with GR Zosky, DJ Turner and PD Sly (Clinical Sciences, TICHR)

A rat model has been employed to study the resident DC populations in the large airways and the nature of the acute changes in their distribution, migration pattern and antigen presenting cell (APC) activity induced as a result of exposure to a locally applied bacterial stimulus. These studies demonstrate a considerably more rapid (and consequently more effectively compartmentalised) response than that which has been observed in recall responses to soluble antigen. Antigen bearing AMDC with competent APC function reached the regional draining lymph node (RLN) within 30 minutes following termination of the bacterial challenge. Importantly, and in contrast to recall responses to non-pathogenic antigens, there is no evidence of local expression of APC activity within the airway mucosa preceding emigration and airways hyper responsiveness (AHR) does not develop. Additionally, we have been able to demonstrate that a subset of airway intraepithelial DC constitutively extend their processes into the airway lumen, thus providing a plausible mechanism for the continuous surveillance of the airway luminal surface and the extremely rapid kinetics of transport of luminal antigenic material to the RLN.

Characterisation of potential antigen presenting cell (APC) progenitor populations within mouse parenchymal lung tissue

DH Strickland, JA Thomas, C von Garnier, PA stumbles and PG Holt

Our recent studies in the mouse, based on morphological, phenotypic and functional characterisations, have revealed the existence of distinct APC populations within parenchymal lung tissue, including macrophages, B cells and DC. Bone marrow repopulation studies using congenic C57BL/6 mice also revealed the possible existence of a population of cells within lung tissue with APC precursor potential. Preliminary investigations to characterise this potential APC progenitor population have focused upon phenotypic and *in vitro* differentiation studies. Limited initial observations are encouraging and suggest that DC precursors are present within lung tissue.

Functional activity of mouse respiratory tract dendritic cell (RT-DC) populations during allergic airway inflammation

C von Garnier, DH Strickland, M Wikstrom, M Smith, JA Thomas, S Napoli, PG Holt, PA Stumbles in collaboration with D Turner, G Zosky and PD Sly (Clinical Sciences, TICHR)

Our previous and on-going studies of respiratory antigen presenting cells (APC) from the conducting airways and lung parenchyma of BALB/c mice have revealed a previously unrecognised diversity based on (i) the co-expression of a range of characteristic cell-surface

proteins, (ii) morphological studies by transmission electron microscopy and (iii) a variety of functional assays. Recent studies, utilising a BALB/c mouse model of experimental allergic asthma in which increased tissue and central airway resistance is observed after aerosol allergen challenge, have focussed on the response of RT-DC as a major subset of cells responsible for initiating and perpetuating allergen-specific T cell immunity in the mucosal tissues of conducting airways. Recent studies have identified a strict compartmentalisation of RT-DC functional changes during the course of the asthmatic response, with activation of airway mucosal RT-DC a distinct feature of the early asthmatic response following aerosol challenge with allergen. *In vivo* analyses have shown a "window" period of between 2 and 12 hours following aerosol challenge during which mucosal RT-DC markedly upregulate the expression of surface (co-stimulatory) molecules involved in T cell activation and also show increased capacity to process inhaled allergen *in vivo* for local presentation to T cells, a process that is strictly controlled in the normal animal. Concurrent comparisons of RT-DC residing in peripheral lung tissue, however, reveal that these cells do not undergo the same functional modification as their mucosal tissue counterparts. These data further highlight the need for future therapeutic strategies to target local events in mucosal tissue at key time-points following allergen exposure in order to regulate aberrant RT-DC and T cell activation.

Respiratory tract dendritic cell phenotype and function following influenza infection

PA Stumbles, M Smith, PG Holt in collaboration with C James (Murdoch University) and D Turner, L Bozanich, PD Sly (Clinical Sciences, TICHR)

Our previous studies of influenza virus infection in adult BALB/c mice identified a period of rapid recruitment and activation of mucosal respiratory tract dendritic cells (RT-DC), peaking at 3 days following infection, as indicated by upregulation of the co-stimulatory molecule CD40 and an increased capacity for ex vivo presentation of antigen. In contrast, RT-DC populations of peripheral lung tissue were much slower to become activated and express CD40, the peak of this response being 14 days following viral infection. Furthermore a distinct feature of the response at this site was the rapid depletion of a population of pulmonary macrophages, indicating that the maintenance of local immunological homeostasis may be significantly disrupted. In particular, studies are underway to determine whether this translates into altered responsiveness to inhaled protein allergens and also the capacity of lung tissue to resist secondary pulmonary bacterial infections which can be a major complication following influenza infection. Further studies have attempted to track the traffic of viral antigens to draining lymph nodes for presentation to viral-specific T cells. These studies indicate that antigen trafficking is restricted to DC of myeloid origin and furthermore, that viral infection has a significant impact on the distribution of other DC subpopulations in lymph node. The impact of these viral-induced effects on the normal immunoregulatory functions occurring within these lymph nodes is currently under investigation.

Co-stimulator blockade in the prevention and therapy of allergic airways disease

L Graca, PG Holt and PA Stumbles in collaboration with H Waldman and S Humm (Oxford University, United Kingdom)

Co-stimulatory molecules are a diverse family of proteins expressed on the surface of antigen presenting cells such as dendritic cells, and include molecules such as CD40, CD80, CD86 as well as a number of others. The primary function of these molecules is to aid in T cell activation following antigen recognition and ensuring that an appropriate immune response ensues. Many studies in experimental model systems have shown that blocking the function of co-stimulatory molecules can lead to altered T cell activation and in some instances result in a state of permanent tolerance, preventing the subsequent activation of T cells in response to further encounters with antigen. The current studies have sought to exploit this principle in order to induce a state of T cell tolerance to inhaled allergens with the hope of either preventing the onset of experimental asthma or treating the symptoms of this disease. Initial studies have focused on blockade of the binding of the co-stimulatory molecule CD40 (expressed on DC) with its ligand (CD40L) expressed on T cells by the use of an anti-CD40L monoclonal antibody (MR-1). Preliminary studies suggest that treatment with the anti-CD40L antibody at the time of first exposure to allergen (sensitisation) can significantly reduce immune reactivity to subsequent allergen challenge by reducing allergen specific antibody production (IgG1) and the extent of allergen-induced eosinophilia. Early studies also suggest a positive effect on improving lung function, however these studies remain to be confirmed. Experiments are also underway to determine whether CD40L blockade can prevent the symptoms of an allergic asthmatic response in animals that have been previously sensitised and also to determine whether combinations of co-stimulatory blockade strategies may be more effective than targeting a single molecule.

Tracking T cell responses to inhaled allergen

M Wikström, M Smith, PG Holt and PA Stumbles

We have been tracking the T cell response to inhaled allergen using adoptive transfer of ovalbumin-specific TCR transgenic $CD4^+$ T cells in mice. In this model, mice sensitised with ovalbumin (OVA) and cholera toxin (CT) develop an eosinophilic inflammatory influx in the lungs when challenged with three daily doses of OVA. In contrast, mice sensitised with OVA, or OVA and LPS, did not. When the lungs were examined after the first challenge dose, there were up to five-fold more OVA-specific T cells producing IL-5 in mice sensitised with OVA and CT. Since IL-5 is crucial for the influx of eosinophils, these IL-5-producing T cells may be critical for the development of eosinophilia. However, there was also an

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increase in the number of IFNγ-producing T cells in mice sensitised with OVA and CT, suggesting that mechanism underlying the development of allergic airways disease is more complex than the preferential activation of Th2 cells in the lungs.

During the course of our studies on the T cell response to daily doses of OVA, we discovered a novel T cell population accumulating in the lungs. They were derived from the OVA-specific $CD4^+$ T cells we were tracking, except they had upregulated expression of the tissue homing molecule, CD103. These cells expressed high levels of the key regulatory molecule FoxP3, suggesting they were a population of regulatory T cells. Interestingly, the proportion of these cells in the lungs appeared to increase with each daily dose of OVA, suggesting they were a direct product of regular allergen exposure. We are continuing to characterise these cells and will explore their influence on inflammation in the lungs.

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Luis Graca *PhD*, Sir William Dunn School of Pathology, University of Oxford, United Kingdom
Christophe von Garnier *MD*, Respiratory Medicine Unit and Department of Internal Medicine, Basel University Hospital, Switzerland

External Committees

International

Patrick Holt. Scientific Advisory Board, Jenner Institute for Vaccine Research, U.K. (1995-current)
Patrick Holt. Councillor, International Society for Mucosal Immunology (1995-current)
Patrick Holt. WHO/IAACI Consulting Group: Primary Prevention of Allergy and Asthma (1999-2004)

National

Patrick Holt. Australian Academy of Sciences: Sectional Committee for Biochemistry, Molecular Biology & Immunology (2002-current)
Philip Stumbles. Member, National Health & Medical Research Council of Australia Training Award Committee

Invited Presentations

Patrick Holt. Symposium Speaker: Developmental regulation of vaccine responsiveness in infancy - International Symposium/Fetschrift for Professor Margaret Burgess, National Centre for Immunisation Research & Surveillance, Sydney.
Patrick Holt. Workshop Speaker: Vaccination and allergic disease: understanding causality and coincidence - First International Neonatal Vaccination Workshop, National Institutes of Health, Washington.
Patrick Holt. Plenary Speaker: Postnatal maturation of immune competence in early childhood and the role of environmental microbial exposure: implications for the pathogenesis of immunologically related diseases - 7th International Congress of the Immunology of Diabetes Society, Cambridge.
Patrick Holt. Meet the Professor Presentation: Regulation of T-cell activation at mucosal surfaces - 7th International Congress of the Immunology

of Diabetes Society, Cambridge.
Patrick Holt. Symposium Speaker: Regulation of the induction and expression of T-cell immunity to environmental allergens in early life - American Thoracic Society Annual Congress, Orlando.
Patrick Holt. Symposium Speaker: Th1-mediated inflammation as a pathogenic factor in allergic disease - 25th Symposium of Collegium Internationale Allergologicum, Bornholm.
Patrick Holt. Plenary Speaker: Immunoregulation of allergy by the innate immune system - the role of Dendritic Cells in the asthma Late Phase Response - XIII Congress of the European Academy of Allergology & Clinical Immunology, Amsterdam.
Patrick Holt. Symposium Speaker and Chair: Allergy Forum - Advances in the immunological background of the atopic child - XIII Congress of the European Academy of Allergology & Clinical Immunology, Amsterdam.
Patrick Holt. Symposium Speaker: Development of allergen-specific T-cell memory in infancy and early childhood - implications for allergic diseases in later life - XIII Congress of the European Academy of Allergology & Clinical Immunology, Amsterdam.
Patrick Holt. Symposium Speaker: Heterogeneity of immune response profiles in atopic children - Annual Meeting of the German National Genome Research Network - Genetic and environmental determinants of allergy and inflammation, Berlin.
Patrick Holt. Symposium Speaker: Role of airway mucosal Dendritic Cells in the asthma Late Phase Response - Annual Meeting of the European Mucosal Immunology Group, Lyon.
Patrick Holt. Symposium Speaker and Chair: Gene expression patterns in human atopic disease - 1st International Conference on Basic and Clinical Immunogenomics, Budapest.
Patrick Holt. Forum Speaker: Recent initiatives in peanut allergy research - US Food Allergy Initiative, New York.
Philip Stumbles. Speaker: Kinetics and function of airway mucosal and peripheral lung dendritic cell subsets during primary influenza infection - 8th International Symposium on Dendritic Cells, Brugge, Belgium.
Philip Stumbles. Speaker: Dynamics of Respiratory Tract Dendritic Cell and Antigen Presenting cell Subsets in Allergic Asthma and Influenza Infection - 12th International Congress of Immunology, Montreal, Canada.
Philip Stumbles. Symposium Chair: Mucosal T cells and Antigen Presenting Cells - 12th International Congress of Immunology, Montreal, Canada.
Philip Stumbles. Speaker: Dendritic Cell Function and T Cell Differentiation in Response to Inhaled Allergens and Pathogens - John Curtin School of Medical Research, Australian National University.

Division of Children's Leukaemia and Cancer Re

Overview

Paediatric cancers are of a much wider spectrum compared to adult cancers, with more than half of them affecting cells of the immune system and the central nervous system, while only a minority involve epithelial cells. Thus, the most common malignancy in children is leukaemia, followed by brain tumours. In order to find better therapies for children with cancer, the Oncology Total Care Unit at Princess Margaret Hospital (PMH) and our division at the institute are both members of the largest study group into these diseases, the US-based Children's Oncology Group (COG).

The research program of the division focuses on childhood leukaemia and brain tumours and comprises three areas. First, it is the identification of genetic alterations which underlie childhood cancers, second, the role of the *HOX11* gene in T-cell acute lymphoblastic leukaemia (T-ALL) and third, the development of a new cancer drug discovery platform. In order to examine the genetic lesions present in the various types of cancer, we make use of the microarray technology to determine gene expression profiles. The initial studies involved our panel of established leukaemia cell lines since they are ideal tools for subsequent testing of potential new drugs for the treatment of patients. Such cell lines are essential for the assessment of agents for future cancer therapy, primarily for *in vitro* studies to identify candidate drugs and in xenograft models to measure drug efficacy *in vivo*. Currently, a large study on primary patient specimens is in progress with the ultimate aim to achieve improved risk stratification for ALL patients and to understand the genetic basis for chemoresistance.

The drug discovery group is directed by Dr Paul Watt and is currently collaborating with Drs E Golemis and I Serebriiski, Fox Chase Cancer Centre, Philadelphia, USA. The team is focused on the use of a reverse two-hybrid screening platform to identify potentially superior cancer drugs. The group has developed a novel genetic system for isolating specific peptide inhibitors of protein interactions that is sufficiently robust for routine industrial application. The system, called '*the discriminator blocker trap*', analyses protein interactions involved in cancer and disease in order to identify peptides that block such interactions and prevent the cancer or disease.
This system is used for drug screening for better therapies for cancer as well as other diseases. It is also a particularly valuable tool in this post-genomic era for the validation of targets involved in multi-protein complexes. The competing knockout mouse or RNAi technologies are unable to selectively eliminate particular complexes of a given protein and therefore are not as useful for the validation of target complexes. Another unique feature of our yeast genetic system is the ability to eliminate low affinity blockers genetically using a titration feature known as the 'affinity filter'. The platform technologies and potential drug leads are currently being developed and commercialised by Phylogica Ltd, the first spin-off company from the Telethon Institute for Child Health Research (http://www.phylogica.com). The company has been assigned the IP portfolio of 8 patent families relating to drug discovery technologies, including patents granted in the USA and Australia, and is to float on the ASX on 30/03/05.

Microarray technology to assess gene expression

Translating microarray data into a diagnostic test for childhood leukaemia

K Hoffmann, AH Beesley and UR Kees in collaboration with MJ Firth and NH de Klerk, Division of Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research

Acute lymphoblastic leukaemia (ALL) is a heterogeneous disease characterised by the presence of several subtypes that can be distinguished based on immunophenotype, differentiation status, as well as chromosomal and molecular abnormalities. The finding that ALL subtypes differ in their response to therapy has greatly facilitated the development of treatments tailored to specific subgroups. In particular, several structural and numerical chromosomal abnormalities are known as independent prognostic factors.
Recent findings from microarray studies have raised the prospect of a standardised diagnostic gene expression platform to enhance accurate diagnosis and risk stratification in ALL. However, the robustness as well as the format for such a diagnostic test remains to be determined. As a step towards clinical application of these findings, we have systematically analysed a published ALL microarray data set from patients at the St. Jude Children's Research Hospital, Memphis (Ross, M.E. et al., Blood 2003, 102: 2951) using Robust Multi-array Analysis (RMA) and Random Forest (RF). We achieved not only very high overall ALL subgroup prediction accuracies of about 98%, but were also able to verify the robustness of these genes in an independent patient cohort diagnosed and treated at the Princess Margaret Hospital for Children. These specimens were analysed in our laboratory and the study established that the selection of discriminating genes is strongly dependent on the analysis method. This may have profound implications for clinical use, particularly when the classifier is reduced to a small set of genes. We have demonstrated that as few as 26 genes yield accurate class prediction, supporting the feasibility of using quantitative RT-PCR for standardised diagnostic testing in paediatric ALL. Importantly, almost 70% of these genes have not been previously identified as essential for class distinction of the six ALL subgroups.

Gene expression levels assessed by oligonucleotide microarray analysis and quantitative real-time RT-PCR - How well do they correlate?

PB Dallas, NG Gottardo, AH Beesley, K Hoffmann, PA Terry, JR Freitas, JM Boag, AJ Cummings, and UR Kees in collaboration with MJ Firth, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research

The use of microarray technology to assess gene expression levels is now widespread in biology. The validation of microarray results using independent mRNA quantitation techniques remains a desirable element of any microarray experiment. To facilitate the comparison of microarray expression data between laboratories it is essential that validation methodologies be critically examined. We have assessed the correlation between expression scores obtained for 48 human genes using oligonucleotide microarrays and the expression levels for the same genes measured by quantitative real-time RT-PCR (qRT-PCR).

Correlations with qRT-PCR data were obtained using microarray data that were processed using robust multi-array analysis (RMA) and the MAS 5.0 algorithm. Our results indicate that when identical transcripts are targeted by the two methods, correlations between qRT-PCR and microarray data are generally strong ($r \geq 0.89$). However, we observed poor correlations between qRT-PCR and RMA or MAS 5.0 normalized microarray data for 13% or 16% of genes, respectively. These results highlight the complementarity of oligonucleotide microarray and qRT-PCR technologies for validation of gene expression measurements, while emphasizing the continuing requirement for caution in interpreting gene expression data.

Genetic alterations in paediatric leukaemia

Prognosis in childhood acute lymphoblastic leukaemia (ALL)

K Hoffmann, NG Gottardo, JR Freitas and UR Kees in collaboration with MJ Firth and NH de Klerk, Division of Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research and DL Baker, Department of Haematology-Oncology, Princess Margaret Hospital, Perth, Western Australia

Despite the high cure rates, resistant forms of childhood ALL constitute a leading cause of cancer-related morbidity and mortality in children. The clinical outcome measured as 5 year event-free survival (EFS) has reached up to 85% for patients classified as standard risk (SR) and 64-75% for high risk (HR) patients. However, a substantial number of patients currently classified and treated as SR patients continue to relapse, highlighting an urgent need for a more comprehensive risk stratification at the time of diagnosis.

To identify prognostic markers that have the potential to discriminate chemotherapy-sensitive (non-relapse) and chemotherapy-resistant (relapse) leukaemia patients at the time of diagnosis, we have generated gene expression profiles from 80 patient specimens using Affymetrix HG-U133A microarrays and analysed the array data using the robust multi-array analysis (RMA) expression measure in combination with a supervised learning algorithm called Random Forest (RF). The initial analysis using hierarchical unsupervised clustering on all probe sets (22,283) separated specimens into their phenotypic groups, T- and B-lineage ALL. Subsequent analyses were conducted separately on the T- and B-lineage subgroups and identified probe sets discriminating between patients who relapsed and those that did not. Importantly, reproducible detection of the differential expression levels of discriminating genes was demonstrated by an independent method, quantitative RT-PCR. Current investigations focus on further verification of discriminating genes identified by microarray analysis using quantitative RT-PCR, validation in independent cohorts of paediatric patients, *in silico* testing using published ALL microarray data sets, and the generation of gene expression profiles from 50 additional specimens using the most recent and comprehensive HG-U133 Plus 2.0 microarrays (54,657 probe sets).

Our findings demonstrate that a comparison of gene expression profiles at the time of diagnosis can identify genes that discriminate chemotherapy-sensitive (non-relapse) and chemotherapy-resistant (relapse) leukaemia specimens. Such a set of genes will be useful in a more risk-based stratification of patients, particularly by recognizing those patients currently classified as SR, who are likely to relapse and would therefore benefit from more intensive therapy.

Gene expression profiling of childhood pre-B acute lymphoblastic leukaemia in comparison to $CD34^+$ haematopoietic stem cells

JM Boag, AH Beesley, AJ Cummings, J Ford, JR Freitas and UR Kees in collaboration with MJ Firth and NH de Klerk, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research

Although the 5-year event free survival for children with acute lymphoblastic leukaemia (ALL) has increased in recent years to 75-90%, many aspects of this disease remain poorly understood. To investigate ALL development and biology, and possibly identify novel drug targets we compared the gene expression patterns of 22 childhood pre-B ALL patient bone marrow (BM) specimens to 5 haematopoietic stem cell samples, enriched from non-malignant BM by CD34 antibody and magnetic bead selection. RNA was extracted from all BM samples and gene expression profiling conducted using HG-133A oligonucleotide microarrays (Affymetrix). Statistical analysis identified the 100 most significantly up and down regulated genes between the ALL and normal specimens. Through extensive data mining we were able to map interactions between greater than 75% of these 200 genes. The gene expression profile was not unique to this analysis as it could be demonstrated in expression data from an independent cohort of 101 pre-B ALL specimens. Additionally, expression levels of eight selected genes were analysed by an independent technique, quantitative RT-PCR, and all genes were found to correlate strongly with respective levels recorded by microarray. To obtain a functional overview, the 200 genes were classified according to the Gene Ontology database. When compared to all genes

represented on the microarray, several functional groups were significantly over-represented, including signal transduction, organogenesis, cell death, lipid metabolism and organic acid metabolism. Many of these genes have previously been implicated in cancer; however, of particular interest was the down regulation of genes concerned with cellular metabolism, specifically those surrounding the citric acid cycle. Further investigation determined that the gene coding for the glucose transport protein GLUT1 was up regulated in the ALL specimens compared to the normal BM specimens. These results provide insight into the altered metabolism of ALL cells and suggest that similar mechanisms operate in both solid cancers and leukaemias. This knowledge may ultimately assist in the identification of more effective treatments for ALL. To ensure our results are not skewed by our choice of normal control tissue, we are currently extending our analysis to include non-malignant pre-B cells ($CD19^+$, IgM^-), obtained from umbilical cord blood.

Gene expression in relapsed childhood acute lymphoblastic leukaemia

AH Beesley, AJ Cummings, JR Freitas, K Hoffmann, and UR Kees in collaboration with MJ Firth and NH de Klerk, Biostatistics and Genetic Epidemiology, Telethon Institute for Child Health Research

Despite tremendous improvements in therapy, resistant forms of childhood acute lymphoblastic leukaemia (ALL) constitute a leading cause of cancer-related deaths in children. The aim of this study was to characterize the genetic profile of leukaemic blasts to better define the biology of relapse and identify new therapeutic targets. RNA was extracted from 11 pairs of cryopreserved pre-B ALL bone marrow specimens (22 in total) taken from the same patients at diagnosis (D) and relapse (R), and analysed using Affymetrix HG-U133A arrays. Data were normalised by Robust Multi-array Analysis (RMA), and the gene expression profiles (D vs. R) compared using a decision-tree based supervised algorithm called Random Forest (RF) that has a built-in reiterative process. The 20 top-ranked genes from this analysis were able to perfectly discriminate between D and R pre-B ALL samples when tested back by hierarchical clustering or principal component analysis. Significantly, the same was found to be true when these genes were tested against independent sets of non-paired pre-B ALL (n=50) and T-ALL (n=22) samples. The only exceptions were two diagnosis T-ALL specimens that were incorrectly identified as R specimens. These particular samples were obtained from patients classified as very high risk at diagnosis, indicating that the selected genes may be a general hallmark of aggressive (or non-responsive) disease. Several of the identified genes have functions relating to multi-drug resistance and their differential expression in relapsed ALL bone marrow is currently being confirmed by both quantitative RT-PCR and comparison with published microarray datasets. Preliminary evidence points towards a potential 'hot-spot' for aberrant gene-expression at the 19p13 chromosomal locus. Experiments are underway to examine the expression of these genes in a panel of leukaemic cell lines for which we have information regarding sensitivity to commonly used chemotherapeutic agents.

The role of *HOX11* in T-cell acute lymphoblastic leukaemia

The search for genes regulated by *HOX11*

DN Dixon, J Ford, UR Kees and WK Greene in collaboration with R Taplin, Division of Science and Engineering, Murdoch University, Perth, Western Australia

HOX11 is a homeobox gene originally identified at a chromosomal breakpoint in T-cell acute lymphoblastic leukemia (T-ALL). It is one of the most frequently deregulated genes in T-ALL, although the precise role of *HOX11* in leukaemogenesis as well as in normal development remains to be further elucidated. *HOX11* encodes a transcription factor that is thought to exert its oncogenic effect through the dysregulation of gene expression. We therefore used cDNA microarray technology to examine the effect of enforced *HOX11* expression on gene transcription in the J2E erythroid cell line. Two novel candidate target genes were identified and confirmed to be differentially expressed in the presence of *HOX11* by Northern blot and/or quantitative RT-PCR. Luciferase reporter assays have further revealed that *HOX11* can transactivate gene transcription from the proximal promoter regions of both of the identified genes. Future studies will seek to determine whether these genes are oncogenically relevant in an attempt to elucidate the mechanism by which this homeobox protein promotes tumorigenesis.

Regulation of FHL1 gene expression by *HOX11*

KL Rice, J Ford, UR Kees and WK Greene

In childhood T-ALL aberrant expression of the homeobox protein *HOX11*, a transcription factor involved in cell fate decisions, is a frequent event. However, the mechanism by which *HOX11* exerts its leukaemogenic effect remains unclear. Previous studies have identified two target genes of *HOX11*, namely aldehyde dehydrogenase 1a1 (Aldh1a1) and Fhl1/Slim1 (Greene et al, 1998). In previous work, we used *ALDH1A1* as model system to dissect the role of *HOX11* in transcriptional regulation and define its responsive element(s). In this study we have mapped the transcriptional start site of *FHL1* and confirmed its target gene status by demonstrating the ability of *HOX11* to transcriptionally regulate the proximal promoter of *FHL1* in luciferase reporter experiments. *FHL1* has potential relevance to tumorigenesis, given that it encodes protein isoforms with suspected roles in transcriptional regulation. This suggests the possibility that the *HOX11* oncoprotein modulates the expression of the *FHL1* gene in a transcriptional cascade, predisposing tumour development.

Paediatric brain cancers

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

PB Dallas, DJ Holthouse, PA Terry, S Egli and UR Kees

Primitive neuroectodermal tumours (PNETs) are the most common type of brain tumour affecting children. Although survival rates for PNET patients have gradually improved over the last 20 years and the prognosis for those classified as average risk is encouraging, the situation for children with high risk PNETs remains dismal. This situation has arisen largely because the molecular biology of PNETs is poorly understood. This lack of knowledge has severely hampered the development of improved treatment strategies that are urgently required.

Chromosomal abnormalities are a common feature of PNET cells, including rearrangements, duplications, deletions, and amplifications. These and other data suggest that multiple genes involved in the coordination of proliferation and differentiation in cells of the developing brain are deregulated during PNET development. As part of the process aimed at identifying these genes, we have analysed chromosomal aberrations in a panel of PNET cell lines using cytogenetic approaches, representational difference analysis (RDA), and microsatellite mapping using 400 markers spread across the entire human genome. This latter work was undertaken in collaboration with the Cancer Genome Project at the Sanger Centre, Cambridge, UK. To further refine our focus to specific regions of the human genome, we have correlated these data with the expression profiles of our five PNET cell lines and a panel of 23 primary PNET specimens, generated using Affymetrix HG-U133A microarrays. These analyses have led to the identification of several genes of interest that function in the regulation of the cell cycle, embryogenesis, and proliferation. In collaboration with Dr Martin Pera and Dr Susan Hawes at the Australian Stem Cell Centre at Monash University we are assessing the roles of these genes in the regulation of proliferation and differentiation of normal human neural stem cells (NSCs), a cell type from which PNETs are thought to arise. The manipulation of target gene expression levels in PNET cell lines and NSCs is being undertaken using adenovirus based overexpression or RNAi knockdown procedures. We anticipate that our studies will lead to a clearer understanding of the molecular pathways involved in PNET pathogenesis, and ultimately to the design of new and improved treatment strategies.

Genomic deletions in cell lines derived from primitive neuroectodermal tumours of the central nervous system

PB Dallas, PA Terry and UR Kees

Extensive genomic deletion affecting a variety of chromosomes is a common finding in primitive neuroectodermal tumours of the central nervous system (CNS-PNETs) implicating the loss of multiple tumour suppressor genes in the pathogenesis of this disease. We have utilized representational difference analysis, microsatellite mapping, and quantitative PCR to identify and verify the presence of genomic deletions on a number of chromosomes in CNS-PNET cell lines. This systematic approach has confirmed the importance of deletions at 10q, 16q, and 17p in PNET pathology and has revealed other regions of deletion that have not been commonly described, e.g. Xq, 1p, 7p, and 13q. These data highlight the prevalence of hemizygous loss in CNS-PNET cells, suggesting that haploinsufficiency affecting multiple tumour suppressor genes may play a fundamental role in CNS-PNET pathogenesis. The identification of specific genes and signalling pathways that are compromised in CNS-PNET cells is crucial for the development of more efficacious and less invasive treatments that are urgently required.

Drug discovery technology

Developing a novel source of structured peptides from natural protein domains

RM Hopkins, NM Milech and PM Watt

Conventional yeast peptide screening normally involves the use of random conformationally constrained 'peptide aptamer' libraries, which typically yield very few successful blockers of protein interactions. We have generated 2 new peptide libraries (Phylomer libraries) that are derived from a bio-diverse set of 19 diverse bacterial genomes in order to capture a diversity of naturally structured sub-domains present within protein sequences. The first, an Interacting Peptide Library consisting of 63 million peptides fused to the B42 activation domain, can be used to isolate peptides capable of binding to a target protein in a forward yeast two hybrid screen. The second is a Blocking Peptide Library made up of over 2 million peptides that can be used to screen for peptides capable of disrupting a specific protein interaction using the reverse two-hybrid system. These 'phylomer' peptides exploit evolution's structural information to enhance the number and affinity of blocking peptides obtained. This increases the probability of identifying high quality leads for potential drug development. These novel peptide libraries are a core part of the drug discovery program, as the source of novel and better drug leads in each of our cancer and disease research projects.

Using the discriminating blocker trap to identify key residues of a target for rational based drug design

PM Watt in collaboration with R Barr and M Bogoyevich, Department Biochemistry, University of Western Australia

Our system has confirmed the interaction of a peptide (named TI-JIP) which interacts with JNK inhibiting its interaction with JUN, its phosphorylation substrate. The work of our collaborator, Dr Bogoyevich at the UWA Biochemistry department, has established that this

peptide can inhibit the enzymatic activity of JNK. When used as the 'bait' for two hybrid screening of two different cDNA libraries TI-JIP did not undergo extensive interactions indicating that its actions are relatively specific towards JNK.

In order to map the domains within JNK required for interaction with TI-JIP, we used mutagenesis of the JNK sequence to generate a library of more than 1 million JNK mutants. These clones were screened using our reverse two-hybrid yeast system (*the discriminating blocker trap*) for mutants that failed to interact with TI-JIP. Sequence analysis of seventeen non-interacting mutants expressing full-length JNK proteins revealed changes to various regions of the JNK molecule. The mutant pool was restricted to those containing five or less mutations and this analysis revealed a series of mutational "hot-spots" on the JNK structure. We have constructed a series of 9 point-mutants to address the importance of these regions and better define the TI-JIP-JNK binding interface. Such a mutation 'hot spot' has been identified which maps to the surface of the JNK protein. This should help clarify the mechanism by which TI-JIP inhibits JNK and might highlight a novel region of JNK to target for drug design.

Targeting telomerase in breast cancer

D Shaw, M Fear and PM Watt in collaboration with P Leedman, Western Australia Institute for Medical Research, Perth, Western Australia

The telomerase holo-complex consists of multiple protein subunits as well as an RNA component to the enzyme. The telomerase complex as a whole elongates the end of chromosomes (telomeres) in cells and prevents cell death. This is required during development, but when telomerase is aberrantly activated in adult cells it leads to tumours. Approximately 90% of human tumours have an active telomerase complex and inhibition of telomerase has been shown to be effective in reducing tumourigenicity. Therefore it is an important potential drug target for the prevention of tumours. A critical component of telomerase activity relies on an interaction between a protein component (hTERT) and an RNA component (hTR). The aim of this project is to use a novel variation on the yeast three-hybrid technique to identify peptides that block the interaction of hTERT and hTR, and thereby prevent telomerase activity. This project combines the novel peptide library with a unique approach to anti-cancer drugs of targeting RNA-Protein interfaces.

The novel screening system is now in place and all components have been tested. An interaction between the two components (hTR and hTERT) can be detected in the yeast and we have successfully selected a positive control blocked interaction from a background of interacting hTR and hTERT. Therefore, the screen for potential therapeutic peptides to block this important interaction is now ready and it is expected that in the coming months peptides will be identified and tested for efficacy in *ex vivo* assays.

Validating protozoa-specific drug targets using peptides from the Phylomer libraries

F Sotzik, RM Hopkins and PM Watt in collaboration with U Ryan and S Reid, Department of Veterinary Biology and Biomedical Science, Murdoch University, Perth, Western Australia

This drug discovery group project is focused on the use of the Phylomer peptides as tools for validating whether the tubulin proteins in certain protozoan parasites are promising targets for drug development. The aims of the project are firstly to identify Phylomer peptides capable of inhibiting dimerisation of α and β tubulin proteins from three protozoan parasites; *Cryptosporidium parvum*, *Trypanosoma brucei* and *Plasmodium falciparum* (the cause of malaria). A forward two-hybrid screen has been used to identify 20 peptides that bind to a-tubulin in *Cryptosporidium parvum*. These peptides are currently being tested to evaluate whether they disrupt a and b tubulin dimerisation.

In addition to identifying peptides that disrupt tubulin dimerisation, this project is also analysing novel methodologies for delivering drugs to protozoans. Initial experiments in this field look promising, suggesting that delivery of anti-protozoan peptides will not be a barrier to drug development. The activity of these anti-tubulin peptides isolated from the yeast screen will be evaluated *in vitro* and *in vivo* against a range of clinical isolates. This will determine whether the tubulin is a good drug target for anti-protozoan drugs, and also whether any of the peptides isolated may be effective anti-protozoan drugs.

Targeting PLZF in acute promyelocytic leukaemia

NM Milech, V Cull, M Fear and PM Watt in collaboration with JD Licht, Mount Sinai School of Medicine, New York NY, USA

PLZF and ETO are both proteins known to be important in promyelocytic leukaemia. This project uses the peptide libraries and the two-hybrid screening platform to identify disruptors of the PLZF-ETO interaction. Due to toxicity issues, full length PLZF and ETO proteins could not be used in our screening system. Therefore we have used specific domains of the interacting proteins to optimise for a reverse two-hybrid screen. More specifically, the PLZF RD2 domain that interacts with ETO was cloned into the bait vector, whilst a truncated ETO containing the PLZF binding site was cloned into the prey vector. These interacting interfaces are suitable for screening, and, together with some minor modifications, the screening system has been improved to allow for simultaneous identification of both high affinity and specific peptide disruptors of the PLZF-ETO interaction.

Screening for phylomer disruptors of the Jun/Jun homodimer interaction

V Cull, DN Dixon, M Fear and PM Watt

Jun-Jun homodimerisation is a critical protein complex involved in neuronal cell death in stroke. Disruption of this complex is likely to yield a potential therapy to reduce brain damage associated with stroke. We have used a reverse-two hybrid approach to isolate peptide blockers of the Jun-Jun homodimer complex. An initial screen of the phylomer peptide library identified 60

potential disruptors of this interaction. Subsequently, 21 of these peptides have been demonstrated to work in a functional assay in mammalian cells, and these peptides are currently being investigated further in more sophisticated models of stroke.

A collaborative grant has recently been obtained, providing the funding for continuing research into these potentially therapeutic peptides. This funding provides the resources for analysing the peptides in both *in vitro* and *in vivo* models of stroke, and to take the most effective peptides through a pre-clinical *in vivo* trial. Importantly for the drug discovery group, a high percentage of the peptides effective in disrupting the Jun dimer are natural peptides. This strongly suggests that the Phylomer peptide libraries we are using as a source of potential drug leads, does indeed contain unique natural peptides that may constitute a novel source of better peptide drugs.

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Research Support

Stewart Cattach
Amanda Gardiner
Reinete Orr

Theses passed

Darcelle Dixon PhD Murdoch University 2004. Identification of downstream target genes of the T-cell oncoprotein HOX11 by global gene expression profiling.
Mansour Heidari PhD Murdoch University 2004. Investigation of the molecular function of the nuclear oncoprotein HOX11 in human T-cell leukaemia.
Nadia Milech PhD University of Western Australia 2004. The role of homeodomain interactions in leukaemia cells.
Kim Rice PhD Murdoch University 2004. Functional analysis of the HOX11 target genes ALDH1A1 and FHL1.

External Committees

International

Ursula Kees. COG-B946, Children's Oncology Group, USA Chair (2000-)
Ursula Kees. COG-B969, Children's Oncology Group, USA Chair (2000-)

Regional

Ursula Kees. Cancer Council of Western Australia
Darcelle Dixon, Mark Fear, Nadia Milech. Australian Society for Medical Research WA, Fundraising and Professional Development Workshop Committee

Invited Presentations

Mark Fear. A Role For Peptides in Drug Discovery. Curtin University, Perth Western Australia, June 2004.
Ursula Kees. Comparison of gene expression signatures in childhood leukaemia. Annual Combined Biological Sciences Meeting, Perth Western Australia, September 2004.
Ursula Kees. Gene Expression Signatures in Paediatric Leukaemia. National Microarray Conference, Perth Western Australia, September 2004.
Ursula Kees. Gene Expression Signatures in Childhood Leukaemia - Current Studies and Future Perspectives. Haematology Society of Australia and New Zealand, Annual Scientific Meeting, Melbourne Australia, October 2004.
Katrin Hoffmann. Gene Expression Profiles in Paediatric Acute Lymphoblastic Leukaemia. Affymetrix Asia Pacific User Group Meeting Singapore, November 2004.
Mark Fear. Potential Neuro-protective Peptides in Stroke. Australian Neuromuscular Research Institute, Sir Charles Gardner Hospital, Perth Western Australia, November 2004.

Acknowledgments

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We thank the Three Boys Legacy, the Variety Club of Western Australia, and the Rotary Club of West Perth for their support of the brain tumour project.

Division of Clinical Sciences

Overview

Much of the work of the Division has revolved around the NH&MRC Asthma Program Grant. This is the third year of the five-year program and has been a year of consolidation and firming up of new collaborations between different groups within the program.

Major projects outside the program include the preparation phase of the first true trial of primary prevention of asthma that will be based on sound immunological theory. This trial using oral mucosal immunoprophylaxis (hence forth known as OMIP) is a major collaborative venture between Peter Sly and Pat Holt (Cell Biology) and further details can be obtained from the Division of Cell Biology report.

The Division is also moving into Environmental Health. Peter Sly and Felicity Flack have been collaborating with the World Health Organization's Children's Environmental Health group for several years. This has led to us applying to become a WHO Collaborating Research Centre for Children's Environmental Health. We are currently well into the designation phase and hope that this venture will be successful in 2005.

Late in 2004 we were successful in obtaining funding from the US Cystic Fibrosis Foundation to determine the optimal methods for the early detection of lung disease in infants and young children with CF. This exciting new program builds on the clinical and research evaluation techniques that we have developed over the last 5-10 years, in conjunction with the Department of Respiratory Medicine at PMH. This three-year project is being conducted in collaboration with Drs. Philip Robinson and Colin Robertson from the Department of Thoracic Medicine, Royal Children's Hospital, Melbourne.

Major achievements from the Asthma Program grant for 2004 include:

Establishment of primary epithelial cell cultures from children with lung diseases. Techniques have been developed for culturing epithelial cells obtained by tracheal brushings from healthy children and those with lung diseases (cystic fibrosis and asthma). Initial studies with these cultures have shown: differences in gene expression in epithelial cells between healthy and asthmatic children; differences in gene expression between asthmatic children and those reported from asthmatic adults; and exaggerated cytokine secretion in children with cystic fibrosis.

Allergen Studies
Development of new models of sustained allergic sensitisation by chronic inhalation of cysteine protease allergens (papain). In addition, key findings have included: demonstration that subjects allergic to aeroallergens have altered immune responses to bacteria as shown by the IgG4 antibody response to the P6 outer membrane protein of Haemophilus influenzae; demonstration that 65% of cat allergic subjects produce IgE antibody to second major (lipocalin) allergen which often binds more IgE than the hitherto only recognized major allergens Fel d 1 and demonstration that allergic subjects have higher T regulatory cell responses to purified mite allergens than non-allergic subjects and major (Der p 1) and less major (Der p 7) allergens induce similar levels.

Physiological assessments
New techniques have been developed for measuring absolute lung volume in mice and for assessing the role of lung volume changes, occurring in disease models, in altering respiratory mechanics. These techniques are being applied in collaborative studies, including the papain model, viral models and studies of interactions between dendritic cells and T-cells in airway walls.

Functional genomics
Studies conducted during the past year have established functional genomics using microarray technology in our group. Initial studies have concentrated on understanding the mechanisms involved in T-cell activation and the differences in these processes in atopic and non-atopic subjects.

The Asthma Program Grant has been very successful in fostering collaborations between the groups involved. The collaborations at Post-doc and RA level have been particularly successful. Examples of these collaborations include:

- Immunogenetics of vaccine responses: Baynam (Le Souef group), Kusel (Sly group), Rowe (Holt group), Holt, Le Souef, Sly
- Epithelial responses to particulate matter exposure: Fonceca (Stick group), Turner (Sly group), Sly, Stick
- Immunological and Physiological responses to pulmonary viral infections: von Garnier (Stumbles group), Turner (Sly group), Stumbles, Holt, Thomas, Sly
- Macrophage and dendritic cell phenotypes and function in cystic fibrosis: Brennan (Sly group), Wikstrom (Holt group), Upham, Sly, Stick, Holt
- Immunological and physiological responses to allergens and to route of exposure: Lenzo (Thomas group), Turner (Sly group), Stumbles, Sly, Holt, Thomas.

New collaborations developed during this year include:

- Dendritic cell interactions with airway epithelium: Kicic (Stick Group), Upham, Stick.
- T-cell regulation of airway hyperresponsiveness: Turner (Sly group), Strickland (Holt group), Sly, Holt.

Respiratory Physiology

The relationship between viral lower respiratory infections in early life and subsequent asthma.

Rachel Collins, Debra Turner, Sam Gard, Zoltan Hantos, Peter Sly.

The aim of this project is to determine

the relationship between viral lower respiratory infections associated with wheeze (wLRI) in early life and the subsequent development of asthma. The two most common causes of wLRI in the first years of life are respiratory syncytial virus (RSV) and parainfluenza (PF) virus. Epidemiological studies have suggested that both viruses can cause abnormal lung function in the short term, but that RSV may be associated with long-term abnormalities of lung function and wheezing. Administration of these viruses in a murine model will enable us to examine whether or not there is scientific support for these epidemiological associations. This is a three year project which forms the basis of Rachel Collins PhD research. The acute and chronic phase of RSV infection have been characterized in mice infected as juveniles (3wk) and adults (8wk). Both adult and juvenile mice were extremely hyperresponsive to bronchoconstrictor challenge at 5 and 7 days post RSV infection. This response had disappeared by 21 days with resolution of infection. The degree of hyperresponsiveness did not correlate with the degree of inflammation in the lungs. Adult mice showed a small but significant increase in cells during the acute phase of infection, however there was no increase in cells in juvenile mice. Long term changes in lung function and airway tone were performed in mice 4, 8, 24 and 34 weeks post infection. Alterations in airway function were progressively evident up to 24 weeks post infection, and had resolved by 34 weeks.

Determining airway hysteresis and tissue properties in mice.

Rachel Collins, Cindy Thamrin, Debra Turner, Zoltan Hantos, Peter Sly.

Mice are becoming increasingly popular for the study of lung diseases, however, informative measures of respiratory mechanics present special challenges. When studying airway diseases, measurements of airway mechanics, including measurements of airway tone are needed to adequately explore disease mechanisms. This study involves the use of adult mice in which respiratory impedance (Z_{RS}) was measured during slow constant-flow inflation and during quasi-exponential relaxed deflation. Oscillatory signals were generated by a loud speaker and delivered to the mice via a wave tube. Various multi-component signals (range 4–38Hz) were evaluated. Mechanical parameters were obtained from single frequencies or by fitting the constant phase model to multi-component spectra. Volume-dependence of airway resistance showed changes consistent with decreased airway tone after deep inspiration, which suggest that airway tone can be successfully measured in mice *in vivo*. Further measurements have successfully been obtained in mice undergoing states of altered airway tone, via administration of methacholine, serotonin (increased tone) or atropine (decreased tone) or by cutting the vagus nerves (decreased tone). The ability to measure airway tone has implications for future measurements of lung mechanics in rodent models of asthma and may also lead to the development of a new technique for determining airway tone in infants.

Mechanisms of respiratory disease following influenza virus infection.

Elizabeth Bozanich, Debra Turner, Sam Gard, Peter Sly, Phil Stumbles.

The aim of this project is to determine the relationship between viral lower respiratory infections associated with wheeze in early life and subsequent asthma. This project runs in parallel with the RSV project discussed above. Influenza virus is an important cause of respiratory morbidity and mortality world-wide, however information is very limited as to the basic mechanisms of the lung disease seen following infection with influenza virus. The hypothesis for this group of studies is that respiratory consequences will be seen in the short term following influenza virus infection but long-term dysregulation of airway function will not be seen. In the parallel studies with RSV, we hypothesise that both short and long term effects will be seen, especially when the infection occurs early in life. Adult (8wk) BALB/c mice were inoculated with influenza A virus (H1N1) and monitored for the duration of the acute phase infection. Clinical illness was induced, measured by weight loss and an assigned clinical score, which was maximal at day 9 post-inoculation and had resolved by day 21. We have mapped the profiles of clinical illness, inflammatory cells, cytokines and the viral load during this time course. Influenza infection was found to elevate baseline airway & tissue mechanics at 4 days post inoculation, with tissue responses persisting into day 9. These changes correspond to the kinetics of viral load & the subsequent clinical symptoms. In 2003, neonates, juveniles and adult mice were assessed for acute responses to influenza infection. In 2004 we characterised the chronic consequences of influenza A infection in mice by measuring lung function and airway hyper-responsiveness 8wks post infection in the three age groups. We found that Influenza did not result in long term changes in baseline lung function or increases in MCh responsiveness in adult mice compared to media controls. A similar pattern was observed in neonate and juvenile mice. Similarly, no significant changes were observed following vagotomy in flu vs control subjects for any age group, which indicates Influenza virus did not alter basal cholinergic tone. Unlike reports in RSV infected models, we found no evidence of long term physiological changes following Influenza A infection in mice.

Assessment of lung volumes in the mouse.

Elizabeth Bozanich, Debra Turner, Zoltan Hantos, Peter Sly

The aim of this project is to develop a technique for measuring lung volume in sedated mice using a custom designed whole body plethysmograph. The measurement of lung volume using plethysmography in humans is complex but well established, it was first described by DuBois et al in 1956 (J Clin Invest 1956;35:322-326). Plethysmography involves placing a person in a chamber and having them take several breaths against a closed shutter using normal breathing. Changes of pressure in the box, brought about by compression and rarefication of the gas within the chamber

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during inspiratory efforts, are related to changes in tidal volume. Plethysmography measures the volume of all the gas in the lungs, including any air trapped by closed or narrow airways, thereby providing a valuable method of measuring absolute lung volume and resting end expiratory lung volume, also known as functional residual capacity (FRC). Lung volume has been shown to alter with disease state, airway smooth muscle constriction, anaesthetic level, inflammation and a number of other factors. Assessment of lung volumes using whole body plethysmography in infants has assisted in the study of normal growth and development of pulmonary function and helped the study of therapeutic intervention in various respiratory diseases. Measurements of FRC have provided valuable information about alteration of lung function in the disease state. In our laboratory we routinely use mice to assess the long and short term influences of allergen, virus and bacteria exposure, fibrosis and bronchoconstrictive agents on the lung, but to date we have not been able to measure lung volume in these murine models of airways disease. Prof Zoltan Hantos, our collaborator and co-worker from Szeged in Hungary, has recently developed a whole body plethysmograph for the mouse. Preliminary studies in Hungary have proved very successful. This year we have replicated these studies in our own laboratory and now aim to incorporate the technique into our routine lung function assessment.

Developmental Changes in Airway and Tissue Mechanics in Mice.

Elizabeth Bozanich, Rachel Collins, Cindy Thamrin, Sam Gard, Zoltán Hantos, Peter D. Sly, Debra J. Turner.

Murine models are used to study many insults to the respiratory and immune system such as viral infections, bacterial exposure and allergen exposure. There is an increasing body of evidence in humans to suggest that early life exposures are important determinants of immunological development and have long-lasting effects on the respiratory system. There is now growing interest in investigating the effects of neonatal exposure to viruses and allergens in the mouse with a view to assessing long-term outcomes. Despite the shift of interest to early life exposures, there is no information to date on the effect of lung growth and development on the mechanical properties of airways and respiratory tissues in mice. Such data will be needed to separate developmental changes following early life exposures from normal maturation. In the present study, we have utilized the low-frequency forced oscillation technique (LFOT) to examine lung function in mice from infancy (2 wks) to adulthood (8wks). LFOT is an advanced measurement of lung function, applying multiple frequencies simultaneously at the airway opening that enables partitioning of the airway and lung tissue mechanics.

We have measured respiratory mechanics at end expiratory pause as well as determining the changes over a wide range of lung volume using a sophisticated system of tracking oscillatory mechanics. We found that airway resistance decreased progressively with age from 2 to 8wk whilst tissue mechanics decreased with age from 2 wk to 5 wk, then plateaued through to 8 wk. This pattern was seen both in measurements taken during end expiratory pause and during slow expiration. These changes in respiratory mechanics parallel the reported structural changes of the murine lung from the postnatal period into adulthood.

The results of our study have several implications for the use of mice as models of human lung diseases. By 5 weeks of age there is little further change with growth in airway mechanics, whereas changes in the mechanical properties are still occurring until 8 weeks of age. This is especially true at lung volumes above end expiration. Most studies that measure lung function do so at forced residual capacity (FRC), either at an end-expiratory pressure set by the ventilator circuit or at Prs of 0 cmH_2O. However, in many experimental circumstances, including during methacholine challenge and in the presence of chronic inflammation, changes in lung volume are likely to occur during the study. These protocol-related changes in lung volume may also be more likely when younger mice are studied. Thus it is important that investigators understand both the age-related and lung volume-dependent changes in respiratory mechanics that may complicate their experimental protocol and take these into account in study design.

Measurement of lung function using broadband forced oscillation.

Cindy Thamrin, Kevin Finucane[1], Bhajan Singh[1], Zoltan Hantos, Peter Sly.[1]
[1] Pulmonary Physiology, Sir Charles Gairdner Hospital

The forced oscillation technique (FOT) is a non-invasive method of measuring lung function, which is advantageous over other pulmonary function tests for studying infants and children in that it requires little or no participation from the subject. Generally, FOT measurements are made at low frequencies below 40 Hz, from which information about the mechanical behaviour of the respiratory system can be obtained. Currently the measurements are averaged over a time period of changing lung volume as the subject breathes. In this project, we seek to find out if useful information can be gained from high frequency (HF) FOT, in particular a HF phenomenon known as antiresonance. Using higher frequencies enables us to develop a method of continuously making FOT measurements over smaller time periods during inspiration, such that we can see how lung function parameters obtained at HF change with lung volume.

In early 2004, we characterised the volume-dependence of HF parameters in a sample of 20 healthy adult humans, and proposed that the decreasing pattern seen is consistent with changes to airway properties during inspiration. In late 2004, via a collaboration with the Dept. of Pulmonary Physiology at Sir Charles Gairdner Hospital, we moved on to investigate if the altered airway properties present in chronic obstructive pulmonary disease could be detected by studying high frequency parameters. Out of 21 COPD patients, it was found that in the

16 subjects who had emphysema, the rate of change of high frequency parameters with lung volume were significantly different compared to healthy subjects. We deduced that high frequency FOT parameters reflect the distortion to airway wall behaviour and airway dimensions present in emphysema.

Murine models of allergic airways inflammation.

Graeme Zosky, Sam Gard, Debra Turner 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 study aims to examine airway hyperresponsiveness (AHR) and airway inflammation in variations of a commonly used mouse model of asthma using ovalbumin (OVA) as the sensitising antigen. Airway hyperresponsiveness to inhaled methacholine (MCh) was assessed using a modification of the forced-oscillation technique (FOT) which is a sophisticated method allowing the separation of changes in respiratory system resistance to flow into airway and parenchymal components. Preliminary results demonstrate that a single OVA challenge induces transient AHR in both the conducting airways and tissue that does not persist beyond 24hrs. Multiple antigen challenges cause massive increases in eosinophil influx into the lungs that translates into AHR that persists until at least 48hrs after the final antigen challenge. This AHR is confined to the parenchyma after three OVA aerosols but is present in both the airways and tissue after six OVA aerosols. Given the massive levels of inflammation associated with multiple OVA challenges, and the fact that a large component of the airway dysfunction in human asthmatics is located in the conducting airways, a single OVA challenge appears to be the most appropriate model to use. Now that we have characterised this model in adult mice we plan to apply these principles in the development of a model of allergic airways sensitisation in neonatal mice. By sensitising mice to a specific antigen as neonates we hope to more accurately mimic the allergic sensitisation of the immature immune system associated with the development of asthma in humans.

Mechanisms of persistent airway inflammation and airway remodeling.

Debra Turner, Neil Carroll[1], Alan James[1], Prof Rakesh Kumar[2]. [1]Pulmonary Physiology, Sir Charles Gairdner Hospital, [2]School of Pathology, University of NSW

The traditional paradigm of allergic inflammation consists of specialised antigen presenting cells presenting antigen to the immune system in organised lymphoid structures (lymph nodes), distant from the airway wall. This relies on a homing of primed lymphocytes back into the airway under the control of a wide range of cytokines, cell specific chemoattractants, adhesion molecules, blood vessels and lymphatic vessels. We propose an alternative mechanism exists by which inflammation may persist and lead to tissue damage and repair (remodeling) via an amplified local response in the airway itself. We postulate that defined lymphoid aggregates (LAs) develop within the airway wall in response to repeated allergen exposure and serve as a local site for antigen presentation and lymphocyte activation, resulting in an increase in inflammatory cells within the airway wall. These cells release pro-inflammatory cytokines and growth factors and subsequently result in altered airway structure and excessive airway narrowing, such is seen in asthma. This project involves assessment of inflammatory cells and LAs in an established ovalbumin-sensitised mouse model[1,2] developed by our collaborator Prof Rakesh Kumar (School of Pathology, University of NSW). In parallel to these studies, post-mortem human asthmatic airway tissues are also being examined. This project will allow us to systematically examine LAs in the bronchial tree and to relate inflammatory, structural and functional changes to local immune reactions following repeated allergen challenges. As such, LAs may be a new target for understanding the immunological basis of asthma. If repeated allergen challenges result in the development of localised inflammation, independent of the draining lymph nodes, intervention in early exposures to allergen may be critical in preventing development of sustained airway inflammation.

This project has been funded by a grant from WAIMR (Western Australian Institute of Medical Research) 2002-2005.

Internal collaborations.

Throughout 2004 we have been involved in several collaborative research projects within the Telethon ICHR. These projects are written up in greater detail elsewhere within this annual report by our collaborators, noted in parenthesis below. In brief we have assessed airway and tissue mechanics in the following collaborative studies;

- Immunomodulatory effects of ultraviolet B (UVB) radiation in mice (with Dr Prue Hart, Division of Molecular Biotechnology)
- Assessment of a new model of allergic sensitisation and immunotherapy induced by intranasal exposure to papain (with Prof Wayne Thomas, Division of Molecular Biotechnology)
- Model Airway mucosal DC maturation is controlled by local T cell interactions following repeated antigen challenge (with Deborah Strickland and Patrick Holt, Division of Cell Biology)
- Characterisation of mouse respiratory tract antigen presenting cell (RT-APC) populations and their response during allergic airway inflammation (Christophe von Garnier and Phil Stumbles, Division of Cell Biology)
- Influenza infection, RT-DC function and the post-natal development of RT-DC network (with Phil Stumbles, Division of Cell Biology)

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Clinical Asthma Studies

Persistence of asthma into adolescence (the WA Pregnancy Cohort)

Peter D. Sly, Patrick G. Holt, Jacquie Joseph Bowen, Lisha van Reyk, Marie Deverell, Merci Kusel, Nick deKlerk.

The WA Pregnancy Cohort is currently undergoing its 13y follow-up (See Population Sciences Report). We are interested in determining the factors that result in asthma persisting into adolescence and adulthood. Epidemiological studies have shown that up to 70% of children with asthma during childhood grow out of their asthma. Asthma associated with atopy is more likely to persist into adult life. However, atopy is much more common that asthma and not all asthmatics who are also atopic have persistent asthma. Longitudinal cohort studies, such as this one, have the potential to allow us to determine the major risk factors for persistent asthma within individuals. When this cohort was seen at the age of six years, the degree of atopy was related to the severity of asthma and seemed to be the most likely factor to predict the persistence of asthma. During the 13y follow-up we are again measuring lung function, bronchial responsiveness and atopy in these children. In addition, we are assessing the response of the hypothalamo-pituitary-adrenal axis to stress, induced by a single breath of a carbon dioxide:oxygen mixture. Blood is also collected for immunological studies (see Cell Biology report). By combing these data with data collected at earlier assessments we will be able to determine the factors that influence the persistence of asthma in children. These data will enable future studies aimed at both primary and secondary prevention of asthma.

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

Merci Kusel, Peter Sly, Pat Holt, Richard Loh

This prospective birth cohort study commenced in 1996 with the recruitment of 263 children at high risk of atopy. Information on all acute respiratory infections experienced by the children in their first 5 years of life were collected, as well as per nasal samples of mucous, during the acute phase of illness. The children underwent venepuncture, skin prick tests and lung function tests at set periods during the course of the study. The first phase of the study was completed in August 2003 and work on identification of the viruses responsible for respiratory infections in the first year of life finalised. Analysis is currently underway to investigate the role of these infections with the development of asthma and atopy.

This unique and important study of respiratory infections, asthma and atopy would not have been possible but for the commitment and tremendous contribution made by the study children and their families.

Is blunted HPA axis a risk factor for asthma and atopy?

Lisha van Reyk, Marie Deverall, Sven Silburn, Merci Kusel, Peter Sly

Epidemiological studies have found associations between stress in early life and atopic diseases such as asthma. The Hypothalamic-Pituitary-Adrenal (HPA) axis, a key neuroendocrine system is activated during times of stress. Evidence suggests that an appropriate HPA-axis response to stressful stimuli is important in the development and control of the immune system. Altered HPA responses have been associated with immune diseases such as rheumatoid arthritis and asthma, and a blunted HPA-axis response to emotional (and possibly physical) stress has been associated with an increased risk of immunologically-mediated diseases, such as asthma. This study has developed and validated the CO2 inhalation test as a suitable method for assessing HPA-axis responses to stress in children. A significant increase in salivary cortisol levels was found after CO2 inhalation. This test is being applied to children from the West Australian Pregnancy cohort who are currently participating in the 12-14 year followup. 818 children have been seen and of these, 45% are atopic and 12.5% have current asthma. The followup of the remainder of the cohort is anticipated to be completed by December 2005.

Their HPA-axis responsiveness will be assessed in the light of their atopic status and history of asthma.

The role of viral lower respiratory infections in allergy and asthma

Hilary Patterson, Cathy Pienaar, Kanokporn Udomittipong, Takayoshi Fukushima, Jenny Tizard, Barbara Holt, Peter Sly.

Studies have found infants hospitalised with RSV bronchiolitis and parainfluenza (PF) can continue to have recurrent episodes of wheeze and a proportion of these children become asthmatics. The influence of viral lower respiratory infections on the development of asthma is controversial. This study aims to determine how RSV/PF alters lung function and also to assess the link between immunological status, infection severity and eventual atopic outcome in the cohort. This study commenced in 2001 and has recruited 105 infants (< 12 months of age) who have been admitted to Princess Margaret Hospital with bronchiolitis or PF. They have been assessed at set intervals in relation to their acute illness. Assessment has included per nasal aspirate, infant lung function during the recovery and post-recovery phases. Symptom history has been collected by questionnaire, and blood samples to determine response to common allergens, as well as genetic predisposition to atopy collected. 93% of the cohort has completed the first post recovery assessment. Parental data collection (spirometry and blood samples) has been completed, with 91% of mothers and 77% of fathers being tested.

Family Asthma Study: asthma exacerbations

Raewyn Mutch, AM Callaghan, GE Kendall, Nicholas De Klerk, Peter Sly.

The Family Asthma Study (FAS) was

undertaken from February 1999 to October 2001 as part of an international collaborative effort funded by Glaxo Smith Kline with the aim of exploring the clinical, genetic and immunological characteristics of allergic sensitization and asthma within families. Families with at least one asthma-affected sibling pair were selected. Of the 763 eligible families initially contacted, 100 families completed formal questionnaire and clinical measures including skin prick testing to 9 common allergens, fraction of exhaled nitric oxide, baseline spirometry, as well as methacholine challenge.

The follow-up study of asthma exacerbations was undertaken in 2004. Of the original FAS cohort, 44.7% of families recruited in 1999, 31.7% of families recruited in 2000 and 71.4% of families recruited in 2001 completed the follow-up study.

Since study participation 46 (22.3%) said their asthma had worsened. 29 (4.9%) visited a doctor, 20 (3.4%) visited a doctor urgently and unexpectedly. 14 (7.3%) sought urgent medical help at least once, 3 (1.6%) sought urgent help at least twice and 2 (1.0%) sought urgent help at least 4 times. 6 had attended an emergency department and 5 had been admitted to hospital, 4 stayed at least 24 hours and 1 required hospitalisation for 5 days; none required intubation. The majority of asthma exacerbations (60%) were triggered by the common cold, followed by viral respiratory infections.

Infant and Preschool Lung function studies

Use of Adenosine Monophosphate (AMP) as a challenge agent in preschool-aged children.

Peter Franklin (SPACH), Takayoshi Fukushima, Catherine Gangell, Graham L. Hall (PMH), Stephen M. Stick (PMH), Peter D. Sly

Wheezing is common in young children and much asthma in preschool-aged children is associated with viral infections. Up to 70% of children grow out of their asthma but it is not always possible to know which children are at increased risk of persistent asthma. We have recently introduced lung function testing, using a forced oscillation technique (FOT) into the clinical management of preschool-aged children with lung diseases. Bronchial challenge with inhaled AMP appears to be related to atopic asthma in older children and adults as it is thought to cause changes in lung function by inducing mast cell degranulation. This project aims to investigate the feasibility of AMP challenges in preschool-aged children and to investigate the clinical utility of such a challenge.

Lung function testing in preschool-aged children with bronchopulmonary dysplasia.

Kanokporn Udomittipong, Graham L. Hall (PMH), Stephen M. Stick (PMH), Peter D. Sly

Children who survive the neonatal period following premature birth and bronchopulmonary dysplasia impose a significant burden on the community. They are at increased risk of further respiratory problems in early childhood. We have recently introduced lung function testing, using a forced oscillation technique (FOT) into the clinical management of preschool-aged children with lung diseases. However, before introducing FOT into the clinical management of children with BPD we need to establish the feasibility and utility of such measurements. This project is investigating the feasibility and reproducibility of FOT in preschool-aged children with BPD and determining whether it can be used to study bronchodilator responses in these children. To date 44 children with BPD have been studied and 35 (80%) successfully completed the FOT studies. The reproducibility was comparable to that seen in healthy preschoolers. Children with BPD had abnormal lung function, both resistance and reactance (see figure) despite being asymptomatic when tested. These abnormalities were corrected by inhaled bronchodilator. The

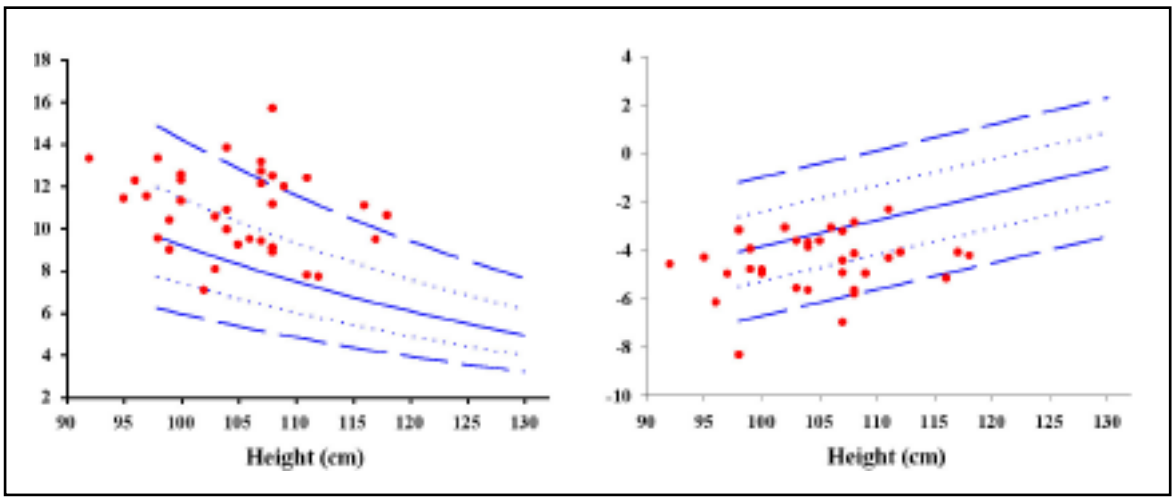

Figure 1

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main predictor of abnormal lung function was the number of days of oxygen therapy the child needed.

These data show the benefits of measuring lung function in preschool-aged children with BPD and suggest that further studies into the possible role of regular bronchodilators are warranted. (See Figure 1)

Clinical Utility of lung function testing using Forced Oscillation in Preschool-aged Children with Cystic Fibrosis.

Catherine Gangell, Graham L Hall (PMH), Hilary Patterson, Siobhain Brennan, Stephen M Stick (PMH), Peter D. Sly

Respiratory disease is the major cause of morbidity and mortality in children with cystic fibrosis. Lung function testing forms a major part of the monitoring of older children with CF. We have recently introduced lung function testing using the forced oscillation technique for preschool-aged children into the assessment of lung disease for this age group. This project aims to determine the clinical utility of using such measurements in the management of preschool-aged children with CF. Results to date suggest that the technique is feasible for use in children with CF as young as 2 years old and that the inherent variability of the tests are the same in children with CF as in age-matched healthy children. Preliminary results also suggest that these tests are sensitive at detecting exacerbations of lung disease. Further studies will be conducted into how well these tests detect the early onset of lung disease in young children with CF.

Cystic Fibrosis

Early detection of inflammation in cystic fibrosis.

Siobhain Brennan, Kaye Winfield, Peter Sly, Steve Stick, Graham Hall, Phil Robinson, Colin Robertson, Sven Thonell

In 2004 this research group continued investigations in the area of early development of inflammation and infection in cystic fibrosis. This project has now been extended to include a site at the Royal Children's' Hospital in Melbourne and has received funding from the US. Cystic Fibrosis Foundation. This project aims to investigate the following:

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

Our findings to date are outlined below:

- Over two hundred and fifty broncho-alveolar lavage fluid samples have been collected from 88 different children with CF. Inflammation is evident in virtually all of the lavage fluids collected, even in the very young infants (from four weeks of age) with no apparent clinical symptoms or infection.
- It appears that once acquired, inflammation consistently tracks with infection.
- The level of acquisition of *Staphylococcus* and *Haemophilus* is lower in this cohort than compared with other national CF centres for the same age group. This may be a consequence of the prophylactic antibiotic policy in the WA paediatric clinic.
- Whilst there appears to be no difference in the age of acquisition in *Pseudomonas* in our clinic compared with the other national CF centers, the lavage program has demonstrated some success at eradicating *Pseudomonas aeruginosa* in young children with CF.

National Hypertonic Saline Trial.

Siobhain Brennan, Elizabeth Balding, Kaye Winfield

In 2001, we participated in the co-ordination of a national trial of inhaled hypertonic saline (NHSCF Trial) as an adjunct therapy for CF. This trial was launched nationally in August 2000, and locally in WA in October 2000, This study has now been finalized and the results from this trial show an small improvements in lung function and considerable improvements in quality of life including reduced hospitalizations and increased attendance at work and school. This is very encouraging as this is an inexpensive complementary treatment with very few side effects. The results of this study have been submitted for publication and are pending review.

Inflammation in cystic fibrosis: Friend or Foe?

Peter Sly, Siobhain Brennan, Kaye Winfield

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

warranted.

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

This study received funding from the National Cystic Fibrosis Association for 2002 and submissions for journals resulting from these studies are currently being compiled.

Dr. Brennan was invited to present results of this study at the European Respiratory Society (ERS). The ERS Young Scientist Award sponsored Dr. Brennan to attend this conference.

Several collaboration have now resulted from this work two of which include:

(1) Investigation of the correlation of urine markers of tissue damage with visual evidence of lung damage using high resolution CT scan, working with Dr. Harm Tiddens of Rotterdam. Dr. Tiddens and his team routinely use HRCT scans to assess early signs of structural lung damage in CF. Dr. Tiddens has included urinary desmosines as an outcome for a trial of treatment for the fungal infection Aspergillus, often found in young children with CF.

(2) Investigation of correlation of biochemical markers of oxidative stress in patients with CF. Working with Dr. Tony Kettle of Christchurch New Zealand, we have established a collaboration to concurrently assess markers of tissue damage alongside established markers of oxidative stress (tyrosine residues). This will provide us with further information about the process of early inflammatory-led damage in children with CF.

Macrolide Therapy for CF lung Disease: Evaluation of Mechanism of Action

Peter Sly, Siobhain Brennan, Kaye Winfield, Gerard Ryan, Phil Robinson

In Collaboration with Abbott Australasia, US collaborators (Prof. Bruce Rubin) and with Sir Charles Gairdner Hospital, and the Royal Childrens Hospital Melbourne, we are co-ordinating the trial of macrolide therapy in the cystic fibrosis community. Macrolides are a class of antibiotics that are not routinely used in cystic fibrosis. The macrolide clarithromycin is being trialed in 90 subjects in total in this study. This study is now completed and results are being compiled. Clarithromycin is being tested for it's ability to reduce inflammation and improve lung function when used in conjunction with current antibiotic therapies. This study has been completed and data analysis is now being conducted by independent statisticians. The results of this trial will be presented in next years' annual report.

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

Siobhain Brennan, John Upham, Matt Wikkstrom, Peter Sly, Steve Stick

In collaboration with Dr. John Upham, of the Cell Biology Division, we are investigating the role of antigen presenting cells in the early stages of cystic fibrosis lung development. This study involves assessment of blood dendritic cells and monocytes, as well as macrophages found in the bronchoalvoelar lavage fluid of children with CF. Children with CF have recurrent infections, which are often difficult to clear and we hypothesise that one reason for this is that there is a dysregulation of the "surveillance" system, which involves the antigen presenting cells in the airways- the dendritic cells and macrophages. With the assistance of the respiratory fellows in respiratory Medicine (Dr. Andrew Martin and colleagues) we use cells from BAL and collect blood from children with CF undergoing BAL, and will also be collecting blood from non-CF children undergoing surgery for non-respiratory related reasons. This study aims to investigate the presence, phenotype and activity of macrophages in the lungs and the presence and activity of dendritic cells and monocytes in the blood using flow cytometry and in-vitro culture techniques.

This study began in late 2003, and received funding from the Australian cystic Fibrosis Research Trust for 2004. The initial findings of this study are being prepared for publication and this work has been used to form the basis of an NHMRC application for 2006.

The Vaccine Trials Group

The Vaccine Trials Group (VTG) was established in 1999 as a collaborative venture involving the Telethon Institute for Child Health Research, Princess Margaret Hospital for Children and the University of Western Australia School of Paediatrics and Child health. Our role is to provide a coordinated approach to the development, delivery, assessment and promotion of vaccines and allergy treatments in our community. The development and use of new, effective vaccines and treatment results in reduced frequency and severity of disease for individuals as well as reducing the overall cost of healthcare. The VTG is involved in epidemiological studies, clinical trials of new and existing vaccines and in basic laboratory research necessary to design to new vaccines. The group is also available as a resource for the public and for health care workers.

New Vaccines for cervical cancer and meningitis

In 2004, the VTG had a busy year with ongoing research in children, adolescents and adults. We started exciting studies of a new vaccine for the prevention of cervical cancer, which is directed against

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the most important strains of the human papilloma virus with studies in adolescent girls and young women looking closely at the safety and the protective antibody responses of this new vaccine. Initial results look very promising and it is expected that the HPV vaccines will be licensed in Australia within the next few years. We have also completed a study of a new combination meningitis vaccine for infants that protects against *Haemophilus influenzae* type b and meningococcal serogroup C and Y infections. This study was the first time the vaccine had been given to infants and was found to induce high levels of protective antibodies and an optimal formulation has been selected for further studies.

Understanding why children develop ear infections

We have also been interested in studying the role of chronic bacterial infection in children with recurrent or chronic ear infections (otitis media) in children requiring ENT surgery. Early results have indicated novel mechanism by which the bacteria may evade the host immune response and lead to the excessive mucus production seen in "glue ear". We have also been looking at whether there are deficiencies in the immune responses in children with recurrent ear infections looking at responses to the common bacteria involved in ear infections as well as to the new pneumococcal vaccine been given to children. These studies have involved children from Perth as well as Aboriginal children from the Northern Territory who have very high rates of chronic ear disease, through collaboration with the Menzies School of Health Research. Understanding the protective immune responses for ear infections will allow us to design better vaccines.

Looking at current vaccines

With the increasing number of vaccines on the immunisation schedule, there have been some concerns raised by anti-vaccination groups about whether this may overload children's immune system. In collaboration with Cell Biology, we investigated whether the measles-mumps rubella and varicella (chickenpox) vaccines might have effects on the developing immune system in toddlers. Reassuringly, we found no evidence of effects of the vaccines on the development of the overall cellular immune responses in these children, confirming the safety of these routine vaccines. We have also been able to establish why some children develop large local reactions to the diphtheria-tetanus-pertussis booster vaccine prior to school entry with evidence of a Th2 pattern cytokine response to the vaccine antigens. This may help us decide the best immunisation schedule or vaccine formulations that will minimise this type of problem. We are also investigating the how well premature infants respond to the next generation of combination vaccines using the Infanrix-hexa vaccine that combines 6 vaccines in one injection. This study is being conducted on children born at KEMH in collaboration with UWS School of Women's and Infant's Health.

Finally it was pleasing to see the decision to introduce a number of new vaccines onto the routine schedule, which had been studied in clinical trials in infants previously by the VTG. The introduction of the pneumococcal conjugate vaccine (Prevenar™) for all infants from January 2005 should have a significant impact on serious pneumococcal infections including meningitis and the new combination vaccines with the injectable polio component will be introduced in late 2005.

Other research

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

Angela Jane Alessandri, Linda Kristjanson, Rev Dr Joseph Parkinson, Peter D Sly

Clinical trials involving children are increasing at a rapid rate as health care professionals strive to determine the best evidence-based treatment regimes for a wide variety of diseases. This has created ethical dilemmas not the least of which is how involved children should be in the consent process. To date there has been little empiric research examining children's needs and desires with respect to information provision and involvement in decision-making in the context of clinical trials. This study is utilising qualitative research methods to document children's current involvement in clinical trial decision-making before examining ways to improve the process. It aims to provide valuable information concerning medical decision-making that may ultimately empower the child and their family in the healthcare setting. The impact of this research will be far reaching as the results will be relevant for both treatment and non-treatment related trials and will be applicable to the entire paediatric community.

The role of psychosocial stress in the development and expression of chronic childhood asthma.

Jackie M Cesareo, Davina French, Sven Silburn, Peter D. Sly.

This project is using longitudinal data collected from the Raine cohort to examine the interactions between psychosocial stress and asthma in chidlren. Specifically, the role stress and family functioning can play in the induction of asthma is a major focus. We are also investigating whehter the psychosocial profile of the child and family can influence the severity of asthma, as well as the effects of persistent asthma on the child and family. Preliminary results suggest that psychosocial stressors play a role in the induction of asthma in children. In addition, 2 year old children who wheeze and who experience stressful life circumstances demonstrate worse asthma when they are 6 years old.

Staff and Students

Head of Division

Peter D Sly MD MBBS DSc FRACP
Professorial Fellow, Department of Paediatrics, The University of Western Australia
Senior Principal Research Fellow, National Health & Medical Research Council
Director, Clinical Research & Education, Princess Margaret Hospital for Children
Respiratory Physician, Princess Margaret Hospital for Children

Research Staff

Elizabeth Bozanich *BSc (Hons)*
Siobhain Brennan *PhD*
Tonia Douglas *MBChB MRCPCH*
Felicity S Flack *PhD*
K.E (Bill) Finucane
Takayoshi Fukushima *MD*
Zoltan Hantos *PhD (Perpetual Visiting Professor)*
Merci Kusel *MBBS PhD*
Hilary Patterson *BE (Hons) BSc*
Cathy Pienaar *BSc (Nursing) MSc (Med)*
Jane Pillow *PhD*
Debra J Turner *PhD*
Kanokporn Udomittipong *MD C.Paed*
Kaye Winfield *BSc*
Graeme Zosky *PhD*

Postgraduate Students

Angela Alessandri *MBBS FRACP (Paeds), MBioeth PhD Candidate*
Jackie M Cesareo *BA (Hons) PhD Candidate (in conjunction with UWA Psychology)*
Rachel A Collins *BSc(Hons) PhD Candidate*
Marie Deverell *BSc (Hons) PhD Candidate*
Tonia Douglas *MBChB (Hons), MRCPCH (UK) PhD Candidate*
Jacqui Joseph-Bowen *BScOT PgradDip (HlthAdmin) MSc (Addiction) PhD Candidate*
Raewyn Mutch *MBChB DipRACOG FRACP PhD Candidate*
Cindy Thamrin *BE (Hons) BSc PhD Candidate*
Lisha van Reyk *BSc Hons PhD Candidate*

Research Support

Cameron Brooke
Samantha Gard *Dip Tech (Applied Science)*
Susan Jamieson *BA*

Theses passed

Jacqui Joseph-Bowen (PhD thesis): The prediction of asthma and allergy in early childhood. Submitted, November 2004.

Awards

Thoracic Society of Australia and New Zealand Travel Award (2004)

- Cindy Thamrin
- Liz Bozanich
- Rachel Collins
- Graeme Zosky

ERS Young Scientist Sponsorship Award (2004): S Brennan
Graeme Zosky – The Telethon ICHR Qantas Young Investigator Award to attend the American Thoracic Society meeting in San Diego, May 2005. Recipient of the Thoracic Society of Australia and New Zealand (WA) poster prize at the annual scientific conference in Mandurah, September 2004.
Cindy Thamrin – UWA Graduates Association Postgraduate Research Travel Award to attend the American Thoracic Society meeting in San Diego, May 2005.
Rachel Collins – John Read prize for physiological research (Australian Lung Foundation & Thoracic Society of Australia and New Zealand), awarded at the TSANZ conference, Sydney, March 2004.

External Committees

International

Peter Sly. Joint American Thoracic Society - European Respiratory Society Task Force on Standards for Infant Respiratory Function Tests.
Peter Sly. European Respiratory Society Task Force on Forced Oscillation
Peter Sly. World Health Organisation advisor on asthma and lung diseases in children
Peter Sly. Long Range Planning Committee, Pediatric Assembly, American Thoracic Society
Peter Sly. International Task Force, Pediatric Assembly, American Thoracic Society

National

Peter Sly. GlaxoSmithKline: Paediatric Asthma Advisory group

Regional

Peter Sly. Asthma Foundation of Western Australia Medical Advisory Committee
Peter Sly. Human Ethics Committee, Princess Margaret Hospital for Children
Peter Sly. Chairman Scientific Advisory Subcommittee, Human Ethics Committee, Princess Margaret Hospital for Children.
Peter Sly. Institute for Child Health Research Executive Committee
Peter Sly. Princess Margaret Hospital Strategic Management Committee
Peter Sly. Research Committee, Arthritis Foundation of WA
R Mutch. Thoracic Society of Australia & New Zealand.
R Collins. TSANZ Associates Subcommittee.
Debra Turner Board of Directors, Scitech, Western Australia

Invited Presentations

- Peter Sly How to design a research project and write a scientific manuscript. Meyer Institute, Florence, September 2004.
- Peter Sly Current thoughts on asthma aetiology and prevention. Johnson & Johnson, New Brunswick, NJ, USA, October 2004.
- Peter Sly. Establishing research collaborations between scientists in developing and developed countries. IPCS/NIEHS Workshop on "promotion of collaborative research between scientists in developed and developing countries". Raleigh-Durham, USA, February 2004.
- Peter Sly. Experience with longitudinal birth cohorts. National Children's Study Workshop, Methods for the Assessment of Asthma-related Health Outcomes. Orlando, USA, May 2004.
- Peter Sly. Summary of Asthma Project. WHO/IPCS Workshop on the expansion of collaborative research networks among scientists in developing and developed countries in the are of gene-environment

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interactions in children. Bangkok, August 2004.

- Peter Sly. In utero exposures. Environmental Influences on the Induction and Incidence of Asthma. USEPA/NIEHS workshop. Research Triangle Park, USA, October 2004.
- Peter Sly. Experience with longitudinal birth cohorts. The WHO 3rd Informal Consultation on Long Term Studies on Environmental Threats to the Health of Children in Developing Countries and Industrialized Countries, Cuernavaca, Mexico, November 2004.
- Peter Sly. How to design a research project and write a scientific manuscript. Meyer Institute, Florence, September 2004.
- Peter Sly. Current thoughts on asthma aetiology and prevention. Johnson & Johnson, New Brunswick, NJ, USA, October 2004.
- Peter Sly. Detection of early lung disease in Cystic Fibrosis. Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Sydney, 2004.
- Peter Sly. Establishing a career path for independent research. Short Course for Respiratory Research, Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Sydney 2004.
- Debra Turner - "Forced oscillation technique (FOT) – from theory to clinical and research applications". Invited presentation at the Thoracic Society of Australia and New Zealand Inaugural Short Course for Respiratory Research. Held on Saturday 20th March 2004, Sydney.
- Siobhain Brennan was invited to present results of Inflammation in cystic fibrosis: Friend or Foe?study at the European Respiratory Society Annual General Meeting 2004 in Glasgow

Division of Molecular Biotechnology

Overview

The current research of the Division of Molecular Biotechnology has focussed on the understanding and treatment of inflammation and allergy. The body's innate and adaptive immune response constitute a major interface with the environment that must function efficiently to ward off infections and malignancies and maintain the correct specificity and balance to avoid harmful allergies and autoimmune conditions. The division undertakes both molecular studies to provide analytical biotechnology and reagents and pathobiological studies to provide the framework and rationale for the investigations. The inflammation group headed by A/Professor Prue Hart has continued to analyse the effects of ultraviolet light exposure on immune responses and study the molecular regulation of inflammatory cytokine responses in macrophages and monocytes. It has discovered that the immunosuppressive effect of UV irradiation acts, not as once thought by interfering with antigen presentation, but by causing an accumulation of regulatory T cells in the lymph nodes. It has also been shown that UV irradiation can decrease the bronchial hyperreactivity typically found in asthmatic responses showing a potential benefit of UV irradiation as well the potential harm associated with decreased immunity. The research on cytokine regulation in inflammation has successfully developed adenovirus transfection systems to introduce genes to modulate the function of different cytokine regulators of human macrophages and monocytes, concentrating on the suppressor of cytokine SOCS3 and the transcription factor STAT3. The allergy group headed by Professor Wayne Thomas has used molecularly cloned allergens to analyse the allergic response to house dust mites. It has demonstrated the importance of the group 1 and 2 allergens in the response of children and their potential for immunotherapeutic targets. As shown by IgG subclass analysis, allergic children make Th1 and Th2 responses to these proteins and not just Th2 responses as previously thought. The immune responses to other allergens are considerably lower for both the Th1 and Th2 compartments. The importance of measuring responses to defined allergen has been demonstrated by the analysis of IgE antibody in an indigenous tropical community. The high titre anti-mite responses were not directed to the typical group 1 and 2 allergens but to another allergen possibly indicating either a cross reactivity or different aetiology of the disease. Similarly responses to newly defined cat allergens will be compared to responses to the well-recognised Fel d 1 allergen. Molecular cloning of allergens and the production of recombinant polypeptides and monoclonal antibodies has been undertaken to provide unique reagents. The development of immunotherapy has concentrated on defining a new mouse model of allergy where the allergic sensitisation like that found for asthma in humans has been induced solely by respiratory exposure. Methods of treatment with peptides representing isolated T or B-cell epitopes continue to be investigated. New phage display technology has been developed to produce blockers of ligand interactions and mimotopes for allergen immunotherapy.

Allergy and Immunology Group

Hierarchical responses to house dust mite allergens

BJ Hales, LA Hazell, W Smith, NNR Chu, LL Do and WR Thomas in collaboration with PG Holt Division of Cell Biology, Telethon Institute for Child Health Research and R Loh Princess Margaret Hospital and PN LeSouef UWA School of Paediatrics and Child Health.

House dust mite allergy results from an immune response to a complex mixture of proteins produced by the mite. One of the key uncertainties in the development of vaccination and immunotherapy is the number and identity of the specificities that are important in the allergy. A solid phase DELFIA (dissociation enhanced lanthanide fluorescence immunoassay have been optimised to accurately measure the response to the different allergens. It has been standardised by quantitative monoclonal antibody capture of the allergen and the use of humanised mouse anti-Der p 2 antibodies (of the IgE, IgG1 and IgG4 subclasses) to construct standard curves. The results with sera from clinically allergic children show that the known major allergens Der p 1 and 2 account for 50% of the total anti-mite IgE antibodies measured whereas low responses were found to Der p 3, 8 and 10 and intermediate responses Der p 4, 5, 7 and 20. This is the first comparative study of this magnitude and accurately demonstrates the importance the Der p 1 and 2 allergens. IgG antibody was essentially only found in the sera of children with IgE responses and it was predominantly restricted to the major allergens Der p 1 and 2. Only occasional and low IgG binding was found to the other allergens. It thus appears that the lack of IgE responses of non-allergic subjects to all allergens, and the lower responses of allergic subjects to non-Der p 1&2 allergens, displays a pattern of lower antigenicity rather than deviated responses regulated away from IgE production. The IgG subclass assays showed that both IgG1 and IgG4 responses which show that the allergic subjects made both Th1 and Th2 responses.

Unexpected specificity of the anti-house dust mite antibody responses in an indigenous tropical population

BJ Hales, LA Hazell and WR Thomas in collaboration with PN LeSouef UWA School of Paediatrics and Child Health

IgE, IgG1 and IgG4 anti-house dust mite antibody binding was measured in sera from as Australian aboriginals from Kalumbaru in northwest Western Australia. Only subjects previously defined as allergic by skin test and IgE assays to house mite extract had IgE antibody but remarkably the IgE titres to the major Der p 1&2 allergens were absent. Instead high titres of antibody were found to the Der p 4 amylase allergen, a specificity of low to intermediate reactivity in other

populations. The responses to the Der p 10 tropomyosin allergen and the Der p 20 arginine kinase allergen were also low contrary to the expectation that the binding may be high because the structure of these allergens is conserved across parasite and insects. The responses to the mites by this population must therefore be an extremely unusual anti-mite response or be the result of cross reactivities to another environmental allergen found in this unusual environment. The IgG1 responses of both subclasses were high for a wide range of the allergens but there was little IgG4 reactivity. This is very different to the responses found in the non-indigenous urban population.

T-regulatory responses in house dust mite allergy

BJ Hales, NNR Chu, LA Hazell and WR Thomas

Peripheral blood mononuclear cells from mite allergic subjects stimulated with the Der p 1 and Der p 7 allergens produced elevated levels of mRNA transcripts of the FOXP3 transcription factor activated in regulatory T cells. This contrasted with the baseline transcripts found in cells from non-allergic subjects stimulated with the allergens and from the transcripts produced by cells from allergic and non-allergic subjects stimulated with the P6 antigen of *Haemophilus influenzae*. This counter-intuitive finding indicates that allergic subjects produce concomitant regulatory and effector responses to the allergens while the response to the bacteria is unregulated, at least by this mechanism. The lack of allergic responses in non-allergic subjects was not a due to the persistence of T-regulatory response. The major allergen Der p 1 induced the same level of FOXP3 transcription as the less important allergen Der p 7 so different levels of T regulation do not associate in a straight forward relationship with low and high responses.

The chitinase allergens of Dermatophagoides pteronyssinus

SE O' Neill, WR Thomas and TK Heinrich

It has previously been documented that dogs and humans in North America produce IgE antibodies to the chitinase and chitinase-like allergens of the mite Dermatophagoides farinae (designated Der p 15 and Der f 18). The role of these potentially important specificities has not been investigated outside a single study or to the more widely distributed species D. pteronyssinus. PCR strategies were used to produce and clone cDNA for the corresponding Der p 15 and Der p 18 allergens. The Der p 15 had the expected level of 85% sequence identity to Der f 15 and contained the repetitive STP sequences found in Der f 15, thought to be the sites for the extensive O-glycosylation of this allergen. An isoallergen or allelic polymorphism with a sequence variation in the STP repeats was found and confirmed to exist in genomic DNA. The Der p 15 was expressed in inclusion bodies of *Escherichia coli* and the resulting polypeptide shown to bind IgE. The Der p 18 allergen also showed the expected 85% sequence identity and like the Der f 18 counterpart did not contain O-glycosylation regions. These proteins are now being expressed in the yeast Pichia pastoris for further analysis of their allergenicity.

The 10B2 epitope of the major mite allergen Der p 2

TK Heinrich, SR Gunn, LA Hazell, BJ Hales and WR Thomas

The 10B2 epitope of Der p 2 is defined by the 10B2 mouse monoclonal antibody. It is mainly constituted by the residues 69-82 of the allergen as determined by the binding of peptides from a T7 bacteriophage C-terminal peptide display library. The epitope is of interest because the small 69-82 peptide not only displayed very strong antibody binding but could also induce high anti-Der p 2 responses when injected into mice. Further studies now show that the same peptide can be isolated as N-terminal fusions with filamentous phage display libraries. This has excluded the possibility that residues N-terminal to the residue 69 of Der p 2 could be important for binding and shows that the N- or C-terminal context of expression of the peptide does affect the antibody binding. Size exclusion chromatography was used to show that the immunogenicity of the fusion polypeptide of the 10B2 epitopes with the glutathione-S-transferase of Schistosoma japonica was not due to aggregates and thus high antibody responses were elicited by a monovalent carrier-peptide complex. Furthermore the fusion was shown to be unable to induce skin anaphylactic responses with the sera of mice immunised with Der p 2. Fusions of some of the sequence variants of the peptides isolated by phage display showed even higher antibody activity than the natural sequences showing that modifications can increase antigenicity. Immunisation studies however showed that despite the increased antigenicity, the modified peptides were poorly immunogenic.

Immunisation with phage displayed peptides

SR Gunn, TK Heinrich and WR Thomas

Phage display provides a method of identifying antigenic peptides with the potential to be used for a wide range of vaccine and immunotherapeutic applications. The peptides can sometimes resemble the primary sequence of the antigenic determinant or be conformational mimics (mimotopes), which form the shape from another sequence. Only a proportion of the peptides have been able to induce useful antibody responses so there is a need to develop techniques to streamline to identify immunogenicity. Studies have been conducted with the synthetic epitope FLAG and the 10B2 epitopes of Der p 2 to optimise methods of inducing immune responses in mice immunised with the phage displaying the peptide. Despite being highly antigenic the FLAG peptide was poorly immunogenic for all protocols tested. The 10B2 epitope of Der p 2 was however immunogenic and the efficacy of the different protocols could be compared. Intraperitoneal injections of phage without adjuvant were the most effective for the N-terminal display of the filamentous phage. Using T7 phage displayed peptides it was shown that the disruption of the phage with the detergent SDS greatly increased the

Division of Molecular Biotechnology

consistency of the antibody response. This technique will be used for the screening of other potentially immunogenic peptides.

Biolistic allergen immunotherapy

WR Thomas in collaboration with PG Holt, PA Stumbles, C van Garnier and JA Thomas Division of Cell Biology, Telethon Institute for Child Health Research, DJ Turner, GR Zosky and PD Sly Division of Clinical Science, Telethon Institute for Child Health Research and MAF Kendall and TJ Mitchell Medical Engineering Unit, Oxford University, UK

Biolistic injection has been developed to shoot particles coated with antigens into the skin. Unlike needle-free fluid jet injections the biolistic procedure is painless and does not cause tissue damage. It is particularly of interest for immunotherapy for allergic disease of children because there is reluctance to inflict the traditional extended course of multiple injections, and the patient compliance is poor. Although the biolistic injections have been examined for vaccination against infectious disease, studies have not been conducted for the down-regulation of immune responses as would be required for allergy. The injected particles lodge almost entirely in the epidermis and thus in intimate proximity to the network of specialised antigen-presenting Langerhans cells, an ideal location for inducing immune responses but not necessarily for regulation. Mice were first sensitised by the injection of ovalbumin in alum and then given a course of subcutaneous biolistic injection of the allergen. They were then boosted with OVA in alum. The IgE responses were profoundly inhibited, as was the ability of respiratory challenge to induce an eosinophilic infiltrate. The IgG1 antibody titres were markedly decreased and the already low IgG2a antibody responses tended to decrease. It was concluded that the biolistic injections induced a downregulation and not immune deviation converting a Th2 to a Th1 response. Respiratory function measured by forced oscillatory technology showed that the biolistic injection initially increased bronchial hyperreactivity as might be expected from the experience with traditional immunotherapy in humans. The hyperreactivity was then decreased to measurements below untreated mice with a significant improvement shown for lung elastance.

Monoclonal antibody production to new newly identified cat allergens

NNR Chu, A Butler, WR Thomas, BJ Hales and W Smith

An investigation of IgE-binding polypeptides produced by cDNA libraries of the cat has revealed the allergenic activity of salivary lipocalin, haptoglobin and the proinflammatory molecule S100A12. To facilitate the investigation of their natural counterparts the recombinant polypeptides have been used to immunise mice and produce monoclonal antibodies. Monoclonal antibodies have been produced to the lipocalin, haptoglobin and S100A12 allergens with the production of antibodies to another recently identified cat allergen cystatin being in progress. As well as being used for environmental monitoring and serological antigen-capture assays, large quantities of the antibodies will be required to affinity purify natural antigens. The use of Celline culture systems for the in vitro production of high titre monoclonal antibodies has been explored as an alternative to ascites production and monoclonal antibody clones have been conditioned for growth in serum-free or reduced serum medium to assist the isolation of the antibodies.

Vaccination and desensitisation of immune responses to the inhalation of papain

JC Lenzo, CE Elliot, PT Cunningham and WR Thomas in collaboration with PG Holt Division of Cell Biology, Telethon Institute for Child Health Research

The ability of the intranasal administration of low doses of papain to induce high and boostable IgE and Th2 responses provides a model to compare traditional and novel methods of vaccination and immunotherapy for allergic disease. Importantly the sensitisation procedure induces the allergy via the respiratory system and without adjuvant. It was shown that vaccination with repeated subcutaneous injections of either aqueous papain or papain absorbed to alum reduced the IgE response to respiratory sensitisation. The prophylactic protocols also reduced the eosinophilic infiltrate following respiratory challenge with allergen and reduced Th1 and Th2 cytokines found in bronchoalveolar lavage fluids. The regulatory IL-10 cytokine was increased. Treatment with the intranasal administration of peptide containing a T-cell epitope of papain could reduce the IgE and lung inflammatory responses of mice immunised subcutaneously with papain in alum but did not affect the IgE responses induced by respiratory sensitisation. It not only failed to control the inflammation induced by allergen challenge to the lung but exacerbated the tissue damage. This was accompanied by increased levels of the inflammatory mediator IL-13. Despite the high success of the subcutaneous protocols for vaccination they did not decrease the allergic responses of mice sensitised before treatment. Sublingual and oral administration administered in a prophylactic protocol have been shown to inhibit the allergic demonstrating for the first time that mucosal tolerance can be used to inhibit responses induced at the respiratory mucosa.

PCR-fragmentation of bacterial genomes

TK Heinrich and WR Thomas in collaboration with PM Watt and RM Hopkins Division of Children's Cancer and Leukaemia Research, Telethon Institute for Child Health Research

Bacterial genomes do not contain introns so gene fragments constitute a source of open reading frames encoding natural peptides containing domains and antigen epitopes. The screening of phage display libraries constructed from random fragments provides a method for identifying ligand binding domains and antigenic specificities. The libraries can additionally be used as a source of structured peptides with potentially stable ligand-binding activities outside of their normal biological function. This strategy is currently being employed to obtain useful ligands for cancer and allergy research

from libraries constructed constituted by a pool of fragments from 25 bacteria with diverse and well-characterised (sequenced) genomes. Because many of the bacteria are unusual organisms that are difficult to grow, a PCR strategy to randomly amplify overlapping fragments of the genome has been adopted. Cycles of extensions from oligonucleotide-tagged random oligonucleotide primers were conducted with Klenow enzyme at low hybridisation stringency. This was followed by cycles of PCR amplification using the oligonucleotide tags as primers. A surprising problem was the difficulty in producing fragments small enough to code for peptides of less than 50 amino acids, and these were considered to be required to pin point and express active sequences. Optimisation of the PCR-based fragmentation was conducted by varying the random oligonucleotide primers, reaction buffers, extension times and clean-up procedures. It achieved the goal although about 150 nucleotides appeared to be the lower limit of the fragmentation with this process. The optimised procedure was found to produced the target range of fragments from 25 species of bacteria and a pool of fragments was cloned into a T7 phage display vector, the cloning of which was verified by sequencing. The library can now be used to isolate peptide ligands by phage display and the procedures that were devised can be used as a general method for producing small gene fragments.

Inflammation Group

Immunomodulatory effects in mice of UVB radiation

PH Hart, JJ Finlay-Jones, S Gorman and J Tan in collaboration with J Thomas and P Stumbles Division of Cell Biology, Telethon Institute for Child Health Research

UVB immunomodulatory effects have been implicated not only in skin cancer development but also in the initiation and progression of autoimmune and infectious diseases in experimental animals. UV rays cannot penetrate beyond the outermost layer of skin. Previous studies by this group when located at the School of Medicine at Flinders University have implicated the dermal mast cell, and its products, in particular histamine, in the mechanisms by which UVB can modulate the immune system. In our studies, the effects of UVB on systemic immunomodulation are studied; the shaved dorsal skin of mice is irradiated whilst the ventral skin provides the site for hapten/antigen sensitisation several days later. The immunomodulatory effects of UVB result in reduced swelling of the ears when they are challenged by surface painting with the same antigen/hapten after a further five days. To better understand the molecular mechanisms involved, lymph node cells draining sites of UVB irradiation and/or hapten sensitisation have been isolated and examined phenotypically and functionally. We initially hypothesised that dendritic cells were altered but using several experimental systems and two different haptens, we have not found any difference in the phenotype or function of these antigen presenting cells from control and UVB-irradiated mice. Our attention turned to other cells in the lymph nodes. We now have evidence that UVB irradiation of mice on their shaved backs for a time equivalent to about 20 minutes in noon in summer in Perth causes an accumulation of regulatory T lymphocytes in skin-draining lymph nodes and these regulatory cells can reduce subsequent immune responses in those nodes. The phenotype and function of these regulatory cells are being further analysed.

Effect of UVB radiation on murine asthma models

PH Hart, J McGlade, WR Thomas and J Lenzo in collaboration with D Turner and G Zosky Division of Clinical Science, Telethon Institute for Child Health Research

We have previously analysed the effect of UVB exposure on models of contact hypersensitivity, a response in mice dependent on type 1 or Th1 immune cells and production of cytokines like interferon-_. The effect of a single exposure to UVB on two asthma models in mice was examined, the expression of these responses being dependent on type 2 or Th2 immune cells and production of cytokines like interleukins-4, –10 and –13. In the first model, mice were UVB-irradiated on their shaved backs three days before sensitisation, resensitisation and challenge intranasally with the cysteine protease, papain. Serum papain-specific IgE levels were reduced by UVB exposure. In the second model, mice were irradiated on their shaved backs three days before sensitisation, and resensitisation, intraperitoneally with ovalbumin mixed with alum. The mice were subsequently challenged by aerolised ovalbumin. Airways hyperreactivity was significantly reduced by exposure to UVB. The levels of inflammatory cytokines in lavage fluid were also reduced. These studies illustrate the systemic effects of UVB administered to one site but affecting immune responses at another, in this case in lungs. 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.

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

PH Hart, JJ Finlay-Jones, M Murcha, C Prele and A Keith-Magee

Due to their phagocytic and poorly proliferative nature, it has been difficult to transfect human monocytes and macrophages isolated from human peripheral blood. This has been a stumbling block for use of primary monocytes and macrophages for study of cytokine signalling pathways relevant to the development and resolution of inflammation. Adenoviral vectors have recently allowed transduction of a high percentage of human macrophages. We have now optimised this methodology in our new Perth laboratory using human monocytes isolated by elutriation from human blood kindly provided by the Perth Red Cross Blood Bank and an adenoviral vector encoding green fluorescent protein (AdV-GFP). After 24 h incubation with M-CSF (20 ng/ml) and a further 24 h incubation with AdV-GFP, only 35% of monocytes express GFP. However,

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centrifugation of these cells with AdV-GFP at 1000 x g for 1 h at 37°C significantly enhances the number of cells expressing GFP (to 65%) and the level of GFP expression per transduced cell (5-fold). The viability of the cells is not compromised. We are particularly interested in the mechanisms by which IL-4 and IL-10 suppress monocyte/macrophage inflammatory cytokine production. We have now completed the cloning of the plasmids for wild type STAT 3 (a potentially important signalling molecule), a dominant negative (mutated) STAT 3, and SOCS 3 (molecule important in regulating cytokine production in mouse macrophages) into the pAdTrack-CMV vectors (which also code for GFP). They were then recombined with the pAdTrack-CMV vector in bacteria before infection of mammalian HEK-293 cells that allowed replication of the virus. We have confirmed expression of all transgenes in human monocytes and macrophages by Western blot. The overexpressed STAT3 is phosphorylated in monocytes incubated with IL-10. Overexpressed SOCS 3 regulates the function of interferon-_ on monocyte TNF production. We are optimising luciferase reporter assays to confirm that the dominant negative form of STAT3 is a true inhibitor of STAT3 transcriptional activity. Preliminary results suggest that the mechanisms by which IL-4 and IL-10 negatively regulate pro-inflammatory mediator production by human monocytes and macrophages may not be the same as those published for murine macrophages.

Cytokine gene polymorphisms in Caucasoid Australian women and risk of preterm birth

PH Hart in collaboration with MA Annells and HM McDonald Women's and Children's Hospital, Adelaide

The relationship between preterm birth (PTB) and 22 single nucleotide polymorphisms in genes encoding cytokines and mediators of apoptosis and host defense has been examined. Caucasoid women (n=202) with a spontaneous PTB <35 weeks have been compared with 185 with term birth(s). Genotyping was performed using the polymerase chain reaction and sequence specific primers. Multivariable analyses included demographic and genetic variables. Analyses suggest that polymorphisms in immunoregulatory genes may influence susceptibility to PTB or PROM. We have recently found polymorphisms in immunoregulatory genes associated with the risk of histologic chorioamnionitis in these Causasoid women.

Tea tree oil effects on skin keratinocytes and fibroblasts

PH Hart, JJ Finlay-Jones and S Nichols in collaboration with A Dharmarajan Anatomy & Human Biology, University of Western Australia, Perth, Western Australia

Whilst the anti-microbial properties of tea tree oil (TTO) are established, the anti-inflammatory properties of TTO are largely anecdotal. Our publications include a description of the effects of TTO on blood monocytes and neutrophils but not on skin cells, which would be the first site exposed to topically applied TTO. Further, it was recently published that TTO may be cytotoxic to melanoma cells. As epidermal cells, both human and mouse keratinocyte cell lines were obtained and cultured with varying concentrations of TTO. Amongst the keratinocyte cell lines, both naturally occurring and UV-induced cell lines were studied, as well as both immunologically-characterised progressor and regressor murine squamous cell carcinoma lines. For dermal cells, primary fibroblasts were grown from mouse skin explants and their responses to TTO compared with those by fibroblast cell lines. TTO at concentrations greater than 0.03% was cytotoxic to all the rapidly proliferating cells *in vitro*. In contrast, TTO at a concentration of 0.125% was not toxic to human blood cells in culture and provides an ongoing challenge for determination of the mechanism of action of TTO. In collaboration with Prof A Dharmarajan, the mechanism by which TTO caused cell apoptosis has been investigated and preliminary studies did not suggest caspase-3 involvement.

Staff and Students

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John Finlay-Jones *PhD*
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April Keith-Magee *BSc MSc* from September
Monika Murcha *PhD* March – October
Cecilia Prele *PhD* from November
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External Committees

WR Thomas. Chairman, International Union of Immunological Societies Allergen Nomenclature Committee
WR Thomas. NHMRC Peer Review Advisory Committee
PH Hart.. Member, NHMRC Inflammation G.R.P. 2C
PH Hart.. Member, Medical Advisory Board, Sylvia & Charles Viertel Charitable Foundation

Invited Presentations

WR Thomas. Recombinant allergens: New diagnostic and therapeutic products. American Academy of Asthma, Allergy and Immunology, Denver 2003
WR Thomas. Clinical trials with recombinant allergens. Seminar. American Academy of Asthma, Allergy and Immunology, San Francisco 2004
WR Thomas. Allergen derived peptides from bench to bedside. Seminar. American Academy of Asthma, Allergy and Immunology, San Francisco 2004
WR Thomas. Successful formulation of genetically engineered vaccines. Hemi-plenary postgraduate lecture. American Academy of Asthma, Allergy and Immunology, San Francisco 2004
WR Thomas. House dust mite allergen vaccines: multi and major allergen-directed strategies. Annual Meeting of Japanese Society of Allergology, Yokohama 2004
WR Thomas. Molecularly defined allergy vaccination. Symposium, Australasian Society for Immunology, Adelaide 2004
PH Hart. Stimuli for mast cell degranulation in UVB-irradiated skin. Keystone Meeting on Mast Cells in Physiology, Host Defense and Disease: beyond IgE. Taos, New Mexico, USA, February 2004
PH Hart. The link between sunlight, mast cells and skin cancer. Stanford University Department Pathology, Stanford, CA, USA March 2004
PH Hart. UVB, mast cells and skin cancer development, American Society for Photobiology, Seattle, WA, USA, July 2004

Division of Population Sciences

The report of the Kulunga Research Network is included in this section

Overview

Population, partnership and prevention

The Division of Population Sciences comprises more than 150 staff and students, who work collaboratively with government, corporate, non-government and community groups to establish determinants of child health and development.

Included in the strengths of the Division are the partnerships that exist between different researchers, the development of synergies between the different research groups and the partnerships developed between students and senior researchers.

The Division is made up of multi-disciplinary teams consisting of epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists.

Scientists and their teams within the Division investigate a wide range of burdensome conditions that affect the developmental health of children. These include: low birth weight, behavioural and mental health problems, autism, obesity and infection. Many projects also have used linked population databases to identify patterns and trends of morbidity and mortality and have explored new ways of measuring and analysing the important influences in whole populations of children, their families and communities.

More specifically, the Division strives to develop preventive strategies that promote and maintain the health and development of children in addition to their social, emotional, academic, and vocational wellbeing.

Some of the main areas of focus for the Division include: Aboriginal health, developmental epidemiology, infectious disease, childhood growth and development, cancer research, and suicide prevention.

Highlights from 2004 included:
February 2004 - Major national study of causes of acute lymphoblastic leukaemia
The Australian study of causes of Acute Lymphoblastic Leukaemia in children is a major national study, which was launched in February 2004. The study is investigating diet, chemical exposure and genetic factors in a bid to unravel the mystery of what causes Acute Lymphoblastic Leukaemia. Funded by the National Health and Medical Research Council, and headquartered at the Telethon Institute, the study is being run in collaboration with children's hospitals and research centres across Australia.

June 2004 - Volume One of the WA Aboriginal Child Health Survey launched
In June 2004, the Western Australian Aboriginal Child Health Survey launched the first volume of findings 'The Health of Aboriginal Children and Young People'. Made possible by funding from Healthway, Lotterywest, Rio Tinto Aboriginal Foundation and the State and Commonwealth Government, the Survey took five years of planning, with two years in the field. Information was collected on more than 5,200 Aboriginal children in Western Australia. The survey also included interviews with 11,300 family members, 2,000 families, and more than 3,000 teachers. It is the most comprehensive survey of Aboriginal children ever undertaken, and details the complexity of factors that contribute to significantly higher rates of death, illness and disability in comparison with other Australians. Findings will be released in five volumes over the next two years.

July 2004 - Major national grant announced
In July 2004, the National Health and Medical Research Council (NHMRC) announced that it would fund the Division of Population Sciences' research program for the next five years at a cost of more than $7 million. The program brings together a multi-disciplinary team of researchers from the Institute, UWA and Curtin University of Technology with the common goals of preventing the major problems facing Australian children and youth today and enhancing their development, health and wellbeing. It aims to develop new ways of measuring and analysing the complex and interacting factors that determine child health in the areas of; social, economic and psychological determinants of health; developmental disorders; growth and nutrition; infection; and Aboriginal health.

July 2004 - ARC Linkage Grant
The Arc Linkage Grant was awarded in July 2004 and will support the ARC Linkage Project. The Linkage Project brings together a number of Industry Partners comprising a number of WA Government Departments including Justice, Community Development, Education and Training, Health and the Disability Services Commission and the University of Western Australia. .The Linkage Project is a large and significant research study, with immense national importance. It will be the first time that a state-wide, whole of population study involving multiple government sectors has been undertaken in Australia. The results of the research will generate valuable information for developing early, holistic intervention strategies to enhance the well-being and life chances of children and young people. The data will also enable a well-integrated strategy for research endeavours that can inform policy, practice, and fiscal decision-making in a rational and evidence-based way.

August 2004 - The Australian Early Development Index launched
The Australian Early Development Index (AEDI): Building Better Communities for Children is a new national project launched, by the Telethon Institute in partnership with the Centre for Community Child Health in Melbourne. Originally developed in Canada, the Early Development Index acts as a measure of how well a community is performing in raising their children. A detailed questionnaire is completed by a teacher in a child's first year of school, measuring social competence; emotional maturity; language and cognitive skills; physical health and wellbeing; and communication skills/general knowledge. The Early Development Index reflects the influence of experiences of the crucial first five

years of life, providing the opportunity for communities to look backward to identify gaps in support and services for children and look forward to adjust childhood and educational services to meet the needs of children. In 2004, the first Australian sites were selected to implement the AEDI in their communities. It is anticipated that by 2007, around 420 schools (12,500 children) would have been involved in the project. The AEDI is funded by the Australian Government Department of Family and Community Development with corporate support from Shell Australia. More information can be found at http://www.australianedi.org.au.

November 2004 - Genetic trigger for Rett Syndrome identified

Researchers at the Children's Hospital at Westmead, working in collaboration with the Telethon Institute and scientists in Adelaide and Wales have identified changes in the gene, serine/threonine kinase 9 (STK9), as being significant in the manifestation of some of the clinical signs associated with disorders such as Rett syndrome and autism. The discovery has important implications for understanding how and why brain function is affected by the disorders, which may lead to the development of possible therapies. Findings were published in the prestigious American Journal of Human Genetics. The Australian research initiative is funded by the Rett Syndrome Australian Research Fund (RSARF), the National Health and Medical Research Council, the Country Women's Association (NSW) and the National Institutes of Health.

December 2004 - First report launched for Intellectual Disability Exploring Answers (IDEA) database

The first report from the new intellectual disability database IDEA - Intellectual Disability Exploring Answers was officially launched in December 2004. The report provides an interesting snapshot of intellectual disability including the fact that the cause of intellectual disability is unknown in a high proportion of cases. IDEA is the most comprehensive database of its kind in the world, using long-term, de-identified data collected by the Disability Services Commission, the Department of Education and Training and the Telethon Institute. The database will be used to help analyse the broad scope of intellectual disability - what causes it, as well as services needs and health issues.

December 2004 - Study finds no long-term harm of repeated prenatal ultrasound examination

The Raine Study, conducted at the Telethon Institute for Child Health Research, has found no long-term harm of repeated prenatal ultrasound examinations during pregnancy. The findings, which received international recognition, are the result of analysis follow-up physical and developmental assessments of Raine Study children at one, two, three, five and eight years of age. The Western Australian Pregnancy Cohort (Raine) Study first began when more than 2,700 women were recruited at 18 weeks in pregnancy from Kind Edward Memorial Hospital between 1988-1991 to examine whether repeated ultrasound had long-term benefits. Half of the study participants were given repeated ultrasound, and the other half were limited to one ultrasound exposure before birth. The study found no significant differences between the two groups at any age as measured by standard tests of childhood speech, language, behaviour and neurological development. The findings were reported in the prestigious British journal The Lancet.

Aboriginal Health Research

Kulunga Research Network

Colleen Hayward, Kate Butler, Heather D'Antoine, Jacinta Johnson, Daniel McAullay

The Kulunga Research Network was established as a joint initiative between TICHR and the WA Aboriginal community (through WAACCHO). The aim of Kulunga is to build capacity in Aboriginal research. In 2004, Kulunga continued to consolidate its communication strategy; namely, circulation grew, and now stands at more than double the circulation from previous years. To further communicate research results, an email distribution list was established, which now includes 50 recipients.

Other notable achievements include:

- Contributing to the development of an Aboriginal Health Promotion Strategy for the WA Health Department. This provided a sound opportunity to apply evidence from the WA Aboriginal Child Health Survey and other Institute data sources to policy development.
- Supporting the Western Australian Aboriginal Child Health Survey, which published its first volume of findings *The Health of Aboriginal Children and Young People.*
- Facilitating a workshop on Indigenous maternal and child health with the Office for Aboriginal and Torres Strait Islander Health at the Royal Perth Hospital's Aboriginal Health Conference in June. The workshop was attended by Aboriginal Health Workers, youth workers, representatives from Aboriginal Community Controlled Health Organisations, and policy makers, and produced some interesting health promotion strategies for, and potential research gaps in Indigenous maternal and child health. These have been presented to both Commonwealth and State health departments.
- Presenting at the World Health Promotion and Education conference in April.
- Supporting the Institute's recently announced Indigenous NHMRC Capacity Building Grant. The grant supports ten Indigenous new researchers who are developed over its five-year term to become independent researchers in their own right. Most are currently undertaking PhD studies, however two are post-doctoral fellows, and two are medical practitioners seeking to consolidate their research expertise. Kulunga coordinates research support and development opportunities for the team.
- Comprehensively reviewing its business plan, brought about by several staffing changes. The review highlighted several areas where effort could be increased, as well as areas requiring adjustment in response to the

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changing environment in Indigenous Affairs.

- Forging international linkages with Kate Butler being successful in attracting an NHMRC Aboriginal and Torres Strait Islander travel sponsorship to visit Canada and New Zealand.
- Completing of the Bunbury Dental Health Project, conducted in conjunction with Kulunga and the South West Aboriginal Medical Service.

Staffing changes have seen our previous Manager, Heather D'Antoine depart to pursue further study. Heather's replacement is Colleen Hayward, comes to us from the Commonwealth Government, and has a wealth of experience in Indigenous affairs and organisational management.
A major goal of the Kulunga Network is to establish core funding.

Swimming Pool project

Impact of swimming pools on children's health in remote Aboriginal communities D Lehmann, M Tennant, D Silva, (Telethon Institute for Child Health Research) H Wright, (Port Hedland Regional Hospital) E Kite, G Merritt (Combined Universities Centre for Rural Health) Kulunga Research Network (ICHR) H Coates, F Lannigan, (Princess Margaret Hospital), and S Weeks (Professional Hearing)

This study has been assessing the effects of swimming pools on the ear and skin health of Aboriginal children in two remote communities. Prevalence of disease has declined over a five year period. The number and severity of skin sores in one community has fallen from 62% in July 2000 before the pool was opened to 18% in August 2004 and in the other from 70% to 34% for the equivalent period. Ear disease has also declined with total number of perforations in both communities dropping from 33% before the pool was opened to 20% in Aug/Sept 2004 (See fgures 1 and 2). Morbidity data from the local medical centre in one community reflects this with a decline in attendance for skin and middle ear infections as well as a reduction in the amount of antibiotics prescribed since the pool was opened.

Rio Tinto Child Health Partnership

Ted Wilkes, Samantha Faulkner, Mary Kepert, Kulunga Research Network

The Rio Tinto Child Health Partnership was developed to deliver improvements in Aboriginal and Torres Strait Islander Child and Maternal Health. It aims to achieve this through the delivery of three projects: modelling the WA Aboriginal Child Health Survey for the NT and QLD; reducing prenatal exposure to alcohol and tobacco; and addressing workforce issues in the early years.

The Partnership is a complex relationship of industry, government and research. The partners include: Rio Tinto, the Alcohol Education Rehabilitation Foundation Limited, WA government, NT government, QLD government and the Telethon Institute for Child Health Research. The Partnership is a five-year project.

TICHR staff involved include Prof Fiona Stanley (Chair National Advisory Committee); Assoc Prof John Finlay Jones, Bob Ginbey, Bruce McHarrie, Lyn Nixon (Corporate and Administrative Division); Assoc Prof Ted Wilkes (Partnership Leader); Colleen Hayward, Kate Butler, Rani Param, Sharde Lee (Kulunga Health Research Network); and Ellen Seymour, Adele Cox, Jacinta Johnson (WAACHS/Project 1 Team) and Mary Kepert.

Western Australian Aboriginal Child Health Survey (WAACHS)

Zubrick S R, Lawrence D M, Silburn S R, Blair E, Milroy H, Wilkes E, Eades S, D'Antoine H, Read A, Ishiguchi P, Doyle S. (2004)
The Western Australian Aboriginal Child Health Survey: The Health of Aboriginal Children and Young People. Telethon Institute for Child Health Research: Perth
ISBN 0-123-456-78910.

The Western Australian Aboriginal Child Health Survey (WAACHS), an extensive state-wide survey of Indigenous children aged 0-17 years, has been undertaken by the TVW Telethon Institute for Child Health Research, Perth, following extensive collaboration and consultation with Aboriginal communities and agencies throughout the State.

The survey, a project of the Kulunga Network at the Institute, has been designed to provide a comprehensive epidemiological "snapshot" of the health, development and wellbeing of Indigenous children in their families and in their schools and communities.

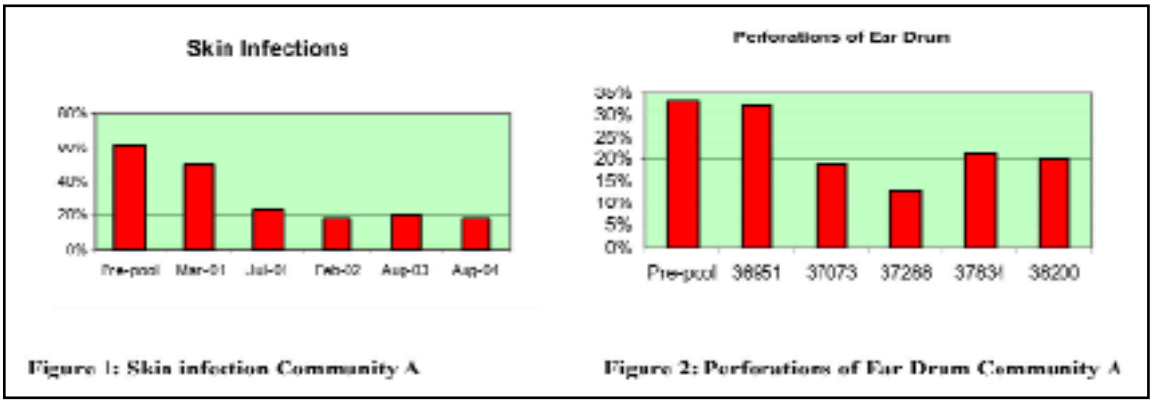

Figure 1: Skin infection Community A

Figure 2: Perforations of Ear Drum Community A

The survey is also notable for the degree to which it seeks to determine some of the factors which promote resilience in Aboriginal young children, exploring both individual and environmental aspects of childhood development. Information has been gathered from caregivers and educators in an endeavour to provide a comprehensive picture of the issues involved, with a sample of 2,000 families and around 5,300 Aboriginal children and young people – about 1 in 6 across the state.

The past year has been a milestone for the team of researchers and writers working on the WAACHS data.

In June 2004 the first volume of results on the physical health of Aboriginal children and young people was launched to significant national and international acclaim. Key findings show that:

- About 48% of Aboriginal people aged 15-19 attend no formal education (vs 24% of non-Aboriginal people)
- Language loss is proceeding at 20% per generation
- Low intergenerational transfer of financial, human and social capital
- No apparent social gradients in health outcomes – not even the relatively "well off" Indigenous families have better child health outcomes

The findings highlight the need to:

- Reduce rates of early teenage pregnancy
- Reduce rates of childhood infectious disease
- Improve nutritional knowledge & access to affordable nutritious food.
- Improve rates of contact of Aboriginal families and children with health services – particularly comprehensive primary health care services.
- Reduce rates of tobacco and alcohol use – particularly in pregnant women.

WAACHS Communication Strategy

In tandem with the release of the first volume of results the, strategy to communicate and disseminate the findings commenced in earnest with WAACHS team members visiting the Pilbara, Goldfields and Kimberley with planned visits to remaining regions in 2005. Keynote presentations were also delivered to the national meeting of the Royal Australian College of Psychiatry (Faculty of Child and Adolescent Psychiatry) in Darwin as well as the Royal Australasian College of Physicians (Chapter of Community Child Health) in Canberra, and the The MHS (The National Mental Health Service Conference) in Brisbane.

In addition to these scientific meetings there have been numerous state and federal policy meetings in which the findings have been presented and discussed to encourage uptake and application.

Currently the WAACHS team is preparing to release the findings for Volume 2 – The Social and Emotional Well Being of Aboriginal Children and Young People – in April 2005. The research team is also supporting the work of "Footprints in Time" – the National Longitudinal Study of Indigenous Children.

Western Australian Mortality Database.

CJ Freemantle, AW Read, NH de Klerk, M Divitini, M Woods, P Cosgrove, Kulunga Research Network, IK Anderson (University of Melbourne), FJ Stanley.

This database, which describes the deaths of every Western Australian born infant, child and young person was constructed by Dr Jane Freemantle This database describes total population linked data and is based on information extracted from the Maternal and Child Health Research Database (MCHRDB). The MCHRDB includes information collected at the time of a child's birth and includes perinatal, maternal and paternal information. These data are linked to a number of administrative and statutory data sets and also disease registries and a number of occasional surveys.

The WA Mortality Database describes the cause, location and circumstances of infant and childhood mortality for all children born in WA between 1980 and 2003 inclusive. Data describing location include the geographical residence at time of birth and of death, the hospital where the death occurred, the actual geographic location of deaths occurring out of hospital. Analysis of this dataset has resulted in the development of a mortality profile, which has described the patterns and trends of infant and childhood mortality in WA over the past 23 years.

There has been a particular focus on measuring the disparities in mortality that exist for Aboriginal children compared to their non-Aboriginal peers. The results have also described the potential antecedents to the excess mortality including the influence of maternal and infants variables on health inequalities.

The disparity in the risk of death for Aboriginal infants (compared with non-Aboriginal) has increased over the past 23 years and in 2002 was over for times higher and for Aboriginal children was over 3 times higher. The main causes of Aboriginal infant death are deaths attributed to Sudden Infant Death Syndrome and infection both causes being potentially preventable. The main causes of childhood deaths and deaths in the teenage and early adulthood were due to accident and injury. These deaths were predominately due to motor vehicle accidents, with suicide being a significant contributor to the deaths of our young WA adults. The rate of death due to suicide among Aboriginal young people was significantly higher than their non-Aboriginal peers.

The rates of death were generally higher among Aboriginal infants born in remote locations, and being born in rural and remote locations was associated with a significantly increased risk of death for Aboriginal infants and children compared with their non-Aboriginal peers.

In 2003, an Advisory Council on the Prevention of Deaths of Children and Young Adults was established by the WA Government to consider preventable deaths in WA and to provide recommendations to the Cabinet

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Standing Committee on Social Policy through the Minister for Community Development. Between 2003 and 2004, Dr Freemantle was the Senior Research Fellow to the Advisory Council and prepared the 1st Annual Report of the Council. This report, "The First Research Report: Patterns and trends of mortality of Western Australian infants, children an young people, 1980-2002", describes the patterns and trends in infant, childhood and young adult mortality in WA over the past 23 years, and included age-specific and cause specific mortality associated with the geographical location of the child at the time of birth and death. It also focused on measuring the disparities that continue to exist in the mortality rate between Aboriginal and non-Aboriginal infants and children. The Council has a focus on preventable deaths and as such data describing SIDS, accident and injury, and suicide were highlighted. The information presented in the First Research Report, has the potential to inform targeted strategies and policies aimed at preventing deaths in WA infants, children and young people.

Qualitative studies of smoking and breast-feeding

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

F Nichols, A Stokes, Jacinta Johnston, C Jeffries-Stokes, D Lehmann in collaboration with Ngunytju Tjitji Pirni Inc and Bega Garnbirringu Health Services Aboriginal Corporation.

As an adjunct to the Kalgoorlie Otitis Media Research Project, a predominantly qualitative study was carried out to investigate maternal smoking and breastfeeding patterns and characteristics as well as Aboriginal perceptions of related social determinants in order to assist in developing appropriate interventions to reduce the high smoking rates and increase duration of breastfeeding. Results were drawn from both a cohort of 280 Aboriginal and non-Aboriginal mothers and a qualitative study which included 55 Aboriginal participants.

In line with national figures, smoking was common among both Aboriginal and non-Aboriginal mothers - with higher rates in the Aboriginal population. Exclusive breastfeeding among Aboriginal mothers was below national and international targets. Study findings pointed consistently to stress (and by way of stress-response, to freedom-seeking behaviour) as a pervasive component in the lives of many Aboriginal people and as a central social determinant in early-weaning and smoking behaviour. Related interventions should therefore include strategies for addressing stress-related causes. Local proposals included multi-faceted young mothers' support, activity and education centres.

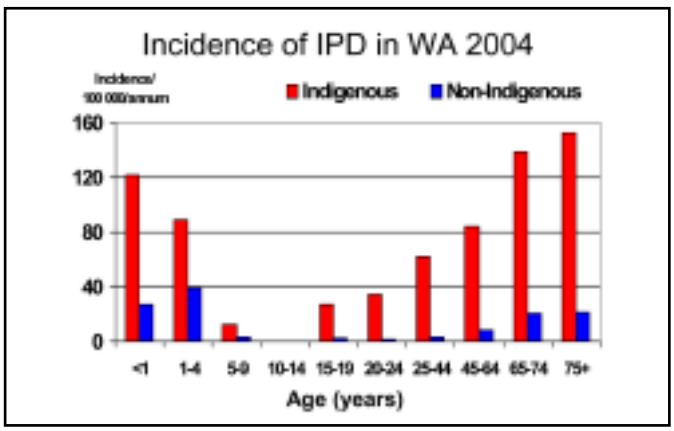

Figure 3

Epidemiology of Infectious Disease

Enhanced Surveillance of Invasive Pneumococcal Disease through the Vaccine Impact Surveillance Network (VISN)

D Lehmann[1], H Moore[1], C Harrison[1], K Rooney[1], L Brown[2], D Murphy[3], T Keil[2], P Richmond[4], C Giele[5], G Dowse5 for the VISN Network.
[1]Telethon Institute for Child Health Research, [2]Department of Microbiology, Princess Margaret Hospital for Children, [3]Public Health Laboratory, Queensland, [4]School of Paediatrics and Child Health, University of Western Australia, [5]WA Department of Health5

The Vaccine Impact Surveillance Network (VISN) was established in 1996 to collect and analyse information on the epidemiology of vaccine-preventable diseases and to evaluate the impact of vaccines and vaccination programs in order to inform policy makers and the general public. Invasive pneumococcal disease (IPD, disease associated with isolation of *Streptococcus pneumoniae* from a normally sterile site such as blood or cerebrospinal fluid) is an important cause of morbidity, mortality, and serious disability and thus a major burden for families and government services. Since 1996 clinical, risk factor and microbiological data have been collected on all reported cases of IPD (primarily pneumonia and meningitis) in Western Australia (WA). IPD became notifiable in 2001. Hospital charts are examined to ascertain clinical diagnosis, management, risk factors and outcome. We determine the serotype and antibiotic resistance of all invasive pneumococcal isolates. Information on pneumococcal vaccination status is sought from the Australian Childhood Immunisation Register and Public Health Units.

In 2004, there were 199 reported cases of IPD and 21 deaths in WA. The highest incidence rates are in the young and the elderly and the Aboriginal population are at much greater risk (see figure). True incidence rates are likely to be even

higher because we may be missing those cases that had to be given antibiotics before blood or CSF could be collected e.g. before transfer of seriously ill people from remote areas.

In 2001, the 7-valent conjugate pneumococcal vaccine (Prevenar™) was licensed for use in Australian children and offered to Aboriginal and other children at high risk of IPD while 23-valent polysaccharide vaccine (Pneumovax™) was offered to children aged >5 yrs and adults at high risk of IPD. From January 2005, all Australian children are being offered Prevenar™ free of charge with a booster of Pneumovax' for Aboriginal and Torres Strait islander children and Pneumovax™ is being offered to all adults aged 65 years or more. VISN will monitor the effectiveness of these vaccines in WA. As part of the Population Sciences' five-year Program Grant awarded this year, IPD data will be linked to the WA Data Linkage System to investigate factors predisposing to IPD and the long-term consequences of IPD. (See figure 3)

Antecedents to hospitalisation with infections in children aged 1month to 2 years

Hospital admissions for infection among Aboriginal and non-Aboriginal children under 2 years of age in Western Australia

K Carville[1], D Lehmann[1], D Burgner[2], N de Klerk[1], G Hall[3], P Jacoby[1], P Richmond[2], TV Riley[4]
[1]Telethon Institute for Child Health Research, [2]School of Paediatrics and Child Health, University of Western Australia, [3]National Centre for Epidemiology and Public Health, [4]Department of Microbiology, University of Western Australia

This study aimed to increase our knowledge about infectious disease morbidity in young Aboriginal and non-Aboriginal children in Western Australia. The study used linked data to examine hospital admissions of all children born in WA from 1st January 1990 to 31st December 2000, followed to 2 years of age. In order to explore causal pathways to infection, an examination of the associations between pregnancy complications and risk of subsequent hospitalisation of the child with infection was conducted.

Infections are responsible for a third of admissions to hospital in children under 2 years of age. Aboriginal children bear a disproportionate burden of infectious disease, however, infection is also a substantial cause of admission to hospital of young non-Aboriginal children. The data show that one in two Aboriginal children were admitted to hospital with an infection at least once, compared with one in five non-Aboriginal children. Some children were admitted more than once, thus the rate of admission for infection was more than four times higher in Aboriginal than non-Aboriginal children. The most common infectious illnesses were bronchiolitis, intestinal infections and upper respiratory tract infections. Aboriginal children were 10 times more likely to be admitted to hospital with skin infections, pneumonia, or bronchitis, and seven times more likely to be admitted with meningitis, compared with non-Aboriginal children. Public health measures are urgently needed to reduce the disproportionately heavy burden of disease among Aboriginal children.

This study also demonstrated an association between some pregnancy complications and the subsequent hospitalisation of young children with infections. We need better understanding of the causal pathways to infection if we wish to develop an evidence base for the most effective interventions. The results do suggest that prevention of complications of pregnancy may lead to a reduction of infections in children under 2 years of age even after the neonatal period.

Neonatal immunisation in PNG

NHMRC/Wellcome International Collaborative Research Grant
Neonatal immunisation with pneumococcal conjugate vaccine in Papua New Guinea

D Lehmann1, J Reeder2, P Holt1, WS Pomat2,3, P Richmond3, A van den Biggelaar1
1Telethon Institute for Child Health Research, 2Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea, 3School of Paediatrics and Child Health, University of Western Australia

Throughout the world an estimated one million children die annually from pneumococcal disease, the majority in early infancy. This study is designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in PNG 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 will assess the impact of PCV on early pneumococcal nasopharyngeal colonisation and on the incidence of acute respiratory infections in the first year of life. We will investigate the development of mucosal and T-cell immunity to non-capsular pneumococcal protein antigens and how this may be affected by early onset of colonisation. The study will also assess the impact of neonatal immunisation on humoral and cellular immune responses to concomitant vaccines (diphtheria toxoid, tetanus toxoid and measles) and whether PCV interferes with normal maturation of the immune system. The project will provide training opportunities for staff from the PNG Institute of Medical Research and for Australian investigators to gain expertise in field research in non-industrialised countries.

We have recruited staff for the clinical and laboratory aspects of the project in PNG and Perth, provided training for two of the Papua New Guinean team in Perth, established a Data Safety Monitoring Board (DSMB) and obtained ethical approval for the project from local and PNG ethics committees. The study proper will begin in 2005.

Non-specific beneficial effects of vaccination in PNG

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

D Lehmann, N de Klerk, M Firth (ICHR) in collaboration with J Vail and MP Alpers

Division of Population Sciences

(Curtin University of Technology)
Following a report of increased risk of death associated with diphtheria tetanus pertussis (DTP) and oral polio vaccination of children living in rural areas of Guinea-Bissau, the World Health Organization Department of Vaccines and Biologicals sought proposals to determine the effects of routine infant immunisation on survival in areas of high mortality. We were awarded a grant to investigate the impact of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. As part of other studies, continuous monthly demographic surveillance enabled us to identify births, deaths, migrations, and immunisation status of all children born in Tari between 1989 and 1994. The study determined the effect of DTP, BCG and measles vaccinations on mortality in the first two years of life and found no deleterious effects of infant immunisations. Our findings have recently been published in an international journal.

Effectiveness of pneumococcal vaccines

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

D Lehmann, N de Klerk, M Firth in collaboration with D Whiting, J Dyke, T Dyke, J Wilson, S Rogers, D Gehala, E Tumbiako, Michael Alpers

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

Causal pathways to Otitis Media

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

D Lehmann, D Elsbury, R Monck, A Stokes, J Finucane, N Pomat, A Arumugaswamy, K Carville, C Jeffries-Stokes in collaboration with D Dunn, P Bonney (Bega Garnbirringu Health Services Aboriginal Corporation), Ngunytju Tjitji Pirni Inc, HLC Coates (Senior ENT Surgeon, Princess Margaret Hospital), TV Riley (Department of Microbiology, University of Western Australia), S Weeks (Audiologist, Professional Hearing Services), AW Cripps (Griffith University, Queensland), J Kyd (Faculty of Applied Science, University of Canberra), J Bowman, A Taylor, D Smith (PathCentre), D Murphy (Public Health Bacteriology Laboratory, Brisbane), N Pingault (Curtin University of Technology).

Otitis media (OM, middle ear infection) can seriously affect childhood development, school performance and subsequent social and economic wellbeing. In order to develop appropriate interventions, Aboriginal and non-Aboriginal newborn babies in the Kalgoorlie-Boulder area were followed regularly until the age of 2 years to investigate causal pathways to OM and to look specifically at demographic, socio-economic, environmental, microbiological and immunological factors putting children at high risk of OM. Field work was completed in December 2004.

The burden of OM remains very high in the Kalgoorlie-Boulder area with a peak prevalence of 72% in Aboriginal children aged 5-9 months and 40% in non-Aboriginal children aged 10-14 months. Twenty-nine percent of Aboriginal and 5% of non-Aboriginal children had a perforated eardrum at least once. Hearing loss was detected in 65% of Aboriginal and 23% of non-Aboriginal at age 12-17 months.

A total of 436 saliva samples (for immunological investigation) and 509 nasopharyngeal specimens (to detect bacteria and viruses in the upper respiratory tract; URT) have been collected from Aboriginal babies and 878 saliva samples and 1050 nasopharyngeal specimens from non-Aboriginal children. Overall carriage rates for *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* were 46%, 38% and 46%, respectively, in Aboriginal children; equivalent carriage rates in non-Aboriginal children were respectively 23%, 11% and 24%. 35% of Aboriginal and 10% of non-Aboriginal babies are colonised with the pneumococcus before the age of 2 months.

We looked at what factors predict early onset of URT pneumococcal carriage since early carriage is known to increase the risk of OM. Crowding (number of people/room) in Aboriginal households and the presence of other children in non-Aboriginal households predicted early pneumococcal carriage. Simultaneous carriage of *H. influenzae* or *M. catarrhalis* also predicted early pneumococcal carriage.

Rhinovirus and adenovirus are the most frequent viruses found in the URT at routine follow-up, more often in Aboriginal than non-Aboriginal babies.

We have found that Aboriginal children exposed to environmental tobacco smoke (ETS) are more than 3 times more likely to develop OM than unexposed children. Aboriginal and non-Aboriginal children living with other children in the household are at increased risk of developing OM and non-Aboriginal boys are more likely to develop OM than girls.

Twins and infectious disease

David Burgner, Katie Donohue, Nick de Klerk, Peter Richmond, Jan Hansen, Marty Firth, Lyn Colvin.

Infectious disease is ever-present in childhood and infection is the commonest hospital admission diagnosis for children but the determinants of infection severity are unknown. We investigated the genetic contribution towards infection susceptibility and ENT procedures by examining infectious hospital admissions in a large twin study.

Zygosity data from the WA Twin Register

were combined with data from unlike sex twins from the Maternal and Child Health Research Database. ICD codes from WA hospital separations were grouped together for specific infectious diagnoses. The effect of zygosity on overall risks of hospital-associated infection and specific infectious diagnoses were examined using case-wise concordance and logistic regression. The effect of zygosity on the correlation between twins in the number of admissions with the same diagnosis was estimated using linear regression after logarithmic transformation.

While concordance for any infectious diagnosis did not differ between DZ and MZ pairs, admission of both twins with the same diagnostic group was significantly increased in MZ pairs. This effect was more marked with extreme phenotypes, where at least one twin was admitted repeatedly with the same diagnosis. Much stronger effects were found when admissions for surgical interventions were examined, particularly for adenotonsillectomy (OR 8.5; 95% CI, 3.7 – 19.6; $p<0.0005$), but zygosity was also significant for admissions with grommet insertion (OR 3.2; 95% CI, 1.7 – 6.1; $p<0.0005$) and adenoidectomy alone (OR 4.3; 95% CI, 2.4 – 7.6; $p<0.0005$). All these effects were independent of gestation, birth weight or gender and suggest that host genetics are important determinants of severity in common infections and that these determinants are disease-specific and are likely to involve loci related to immune function, allergy and facial structure. Understanding the biological pathways underpinning these observations will direct innovative strategies for prevention of these common and costly childhood conditions.

Further work is continuing by expanding the project to examine these associations within sibs as well as twins.

Developmental Epidemiology

Rascals (Randomly Ascertained Sample of Children in Australia's Largest State)

SR Zubrick, SR Silburn, JJ Kurinczuk (University of Oxford, UK), G Dixon, DE Parsons, S Dragovic, K Moore, PR Burton (University of Leicester, UK), in collaboration with VP Dawes (formerly the Health Department of Western Australia), AJ Plant (Curtin University).

The RASCALS Study (formerly known as the Western Australian Pregnancy and Infancy Survey) was initiated in 1995 whereby a 10% random sample of all mothers in Western Australia who recently delivered a live born baby between January 1995 and June 1997 were selected to participate in a self-completion survey. Of the 6019 mothers who were mailed a questionnaire, an outstanding 82% of the questionnaires were returned completed. From this sample base a group of caregivers continue to be followed up annually at the time of the study child's birthday. The information initially collected was used in the evaluation of health promotion and disease prevention services and centred on the mother's behaviour before, during, and after pregnancy. The initial survey included questions on rubella immunisation, folic acid intake, SIDS risk factors, infant feeding practices, cigarette smoking, alcohol consumption, infertility, family composition and so on. Subsequent follow-up concentrated on parental and disciplinary practices, maternal and paternal employment, family composition and on-going assessment of both the study child's and primary caregiver's mental well-being.

Associate Professor Wendy Hall from the University of British Columbia Canada has been analysing some of the data on sleep patterns. In July 2002 she presented some of the findings on sleep at the Third International Conference on Child and Adolescent Mental Health in Brisbane and is in the process of submitting a paper to a journal for publication.

Associate Professor Kate Taylor and her colleagues were awarded a $6 million dollar research grant from the USA National Institutes of Health to study speech and language in children and are using data from the RASCALS study. 237 RASCALS children and 197 of their family members (parents and brothers and sisters) are now taking part in the LOOKING at Language study.

Associate Professor Leon Straker from Curtin University of Technology Western Australia is analysing the RASCALS data on children's computer use and the following paper has been written – "Health outcomes associated with increased information and communications technology exposure in 5 year olds" by Straker, Pollock, Zubrick and Kurinczuk.

Dr Linda Slack-Smith, a senior lecturer in the School of Population Health at the University of Western Australia is conducting a project using data from the RASCALS study to investigate children's dental visits. Information on dental visits was collected in the six-year questionnaire and is currently being analysed. Preliminary results have been presented at a national dental research conference in Melbourne in 2003.

Birth Defects - Folate

Neural Tube Defects

Carol Bower, Jan Payne, Peta Serna, Marg Miller, Fiona Stanley, Heather D'Antoine, Sandy Eades

There has been activity on several fronts during 2004 in relation to neural tube defects research.

We contributed data to a submission to Food Standards Australia and New Zealand in consideration of mandatory fortification of food with folate. Fortification of food with folate in Australia and New Zealand is now receiving priority consideration, through a process of review, public consultation and reporting. Based on the data in the submission, a short report was produced, that was published in *Birth Defects Research*.

Division of Population Sciences

Two studies of neural tube defects were also published in 2004.

1. Folate promotion in Western Australia and the prevention of neural tube defects
This was a case control study, in which the mothers of 36 cases of neural tube defects and 528 controls (with no birth defects) participated (79% response rate). Participating mothers completed two questionnaires – one about their pregnancy, and another related to diet. About a third of women reported taking folic acid supplements periconceptionally, and use of folic acid supplements was associated with a small reduction in risk of neural tube defects. For the women not taking supplements, high levels of dietary folate provided some protection, and most women obtained at least some daily folate from fortified foods. These results underscore the need for greater promotion of folic acid supplementation and greater knowledge and consumption of foods fortified with folate. As fortification is only voluntary at present in Australia, mandatory fortification could be expected to provide greater protection against neural tube defects than is currently occurring with voluntary fortification.

Further work using the data on controls in this study showed that about 60% of control women were aware of the correct association between folate and prevention of neural tube defects before pregnancy, slightly less than a third reported taking 200µg or more of folic acid from supplements daily in the periconceptional period and just over half obtained 100µg or more of folic acid from fortified foods. Women who were unaware of the correct message before pregnancy were more likely than women who were aware of the message before pregnancy to be younger, having their first pregnancy, be single or in a de facto relationship, have no tertiary education, and be a public patient. Similar associations were seen for women taking less than 200µg of folic acid in supplements daily in the periconceptional period. There were no significant associations between these demographic variables and amount of folate obtained from fortified foods. Women who were unaware of the correct message and women who did not take folic acid supplements were more likely to have smoked, not to have engaged in exercise, and not to have planned their pregnancy, whereas there was no association with these behavioural characteristics and intake of folate from fortified foods. These results indicate that health promotion strategies have not reached all segments of the target population equally, but there is no such disparity with folate-fortified foods, and they suggest that mandatory fortification of a staple food is likely to reach all women regardless of demographic and behavioural characteristics, and hence provide improved opportunity for prevention of neural tube defects in Australia.

2. Neural tube defects in Indigenous and non-Indigenous infants
From some previous work we knew that neural tube defects were around 40% more common in Indigenous compared with non-Indigenous infants in WA. We had also documented a fall in neural tube defects as a result of health promotion of periconceptional folic acid supplement use (begun in 1993) and voluntary fortification of food with folate (this began in 1996). We undertook this study in order to determine whether the reduction in neural tube defects had occurred in both Indigenous and non-Indigenous populations. Birth years were grouped: 1980-1992 (pre-health promotion); 1993-1995 (health promotion but no fortification); and 1996-2000 (health promotion and fortification). From the graph below, compared with the pre-promotion period, it can be seen that in non-Indigenous infants, there was a fall in neural tube defects in the final period, but not for Indigenous infants. The prevalence ratio (PR), comparing Indigenous with non-Indigenous rates in 1980-1992 was 1.42. It was 1.69 in 1993-1995 and 1.98 in 1996-2000. The confidence intervals around all these ratios excluded unity. Thus, from being 40% more common prior to health promotion of folate and voluntary food fortification, neural tube defects are now almost twice as common in Indigenous compared with non-Indigenous infants, and there has been no reduction in rates for Indigenous infants over the period when health promotion and voluntary fortification have been in place. This is further evidence to support mandatory fortification with folate of a food that is consumed regularly by both Indigenous and non-Indigenous women. (See figure 4)

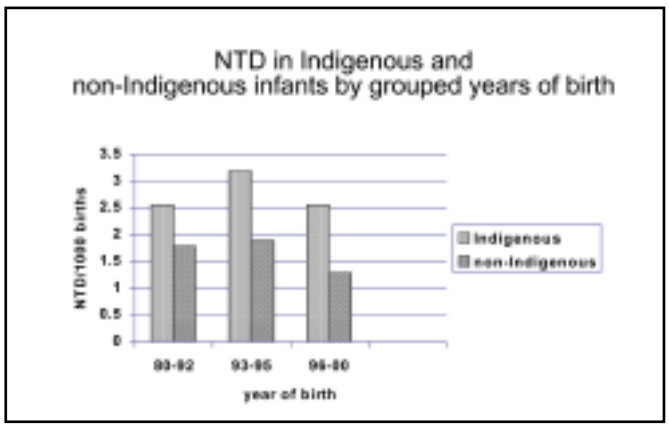

Figure 4

Fetal Alcohol Syndrome

Carol Bower, Elizabeth Elliott, Eric Haan, Jan Payne, Heather D'Antoine, Colleen O'Leary, Lyn Colvin, Tracy Barker, Kulunga Research Network

2004 was the third and final year of our Healthway grant to study Fetal Alcohol Syndrome in Australia.

Fetal alcohol syndrome (FAS) was first identified in the 1970s and has been described as a preventable tragedy. FAS is caused by maternal alcohol consumption

during pregnancy and represents the severe end of the spectrum of the effects of exposure to alcohol *in utero*. Children with FAS display a wide range of physical defects and disabilities, however the cardinal features are:

- Minor cranio-facial abnormalities
- Prenatal and/or postnatal growth deficiency
- Damage to the central nervous system.

A definite diagnosis of FAS requires identification of all of these features as well as confirmation of prenatal alcohol exposure.

Most epidemiological studies on FAS have been performed in the USA and Canada where birth prevalence estimates range from 0.26-7.2 per 1,000 live births, and in the Western Cape Province in South Africa (39 per 1,000 births). However, data from the Western Australian Birth Defects Registry (1987-1997) suggest a birth prevalence of 0.18 per 1,000 live births (0.02 per 1,000 non-Indigenous births; 2.76 per 1,000 Indigenous births), and a study of children born in the Northern Territory (1990-2000) estimated a birth prevalence of 0.68 per 1,000 live births (1.9 per 1,000 Indigenous live births).

Over the three years of this study we have conducted national surveillance of FAS through the Australian Paediatric Surveillance Unit (APSU) and have identified 53 children under 15 years of age with newly diagnosed FAS. The median age of children with FAS at the time of diagnosis was 2.8 years (range newborn to 12 years), 29/53 (55%) were male, and 28/53 (53%) were identified as Indigenous although information on Indigenous status was not available for five children. Children with FAS were reported from all States except Tasmania.

The highest level of education attained by mothers of children with FAS was primary school for 8/53 (15%) and secondary school for 17/53 (32%). Information on the highest level of education was not available for 27/53 (51%). 14/53 (26%) children with FAS had siblings affected with FAS but for 21/53 (40%) information about their siblings was not available. Only 22/53 (42%) of the children with FAS were living with their biological parent(s), 7/53 (13%) with their grandparents or other relative, and 23/53 (43%) were adopted or fostered.

38/53 (72%) of children with FAS were exposed to other substances in utero, including nicotine 35 (66%), cocaine (1), heroin (3), glue or solvents (2), marijuana 14 (26%), and other drugs including carbamazepine, benzodiazepines, naltrexone, sodium valproate, morphine, pethidine, amphetamine and chlorpromazine.

All of the children diagnosed with FAS had been referred to health related agencies including specialty paediatric services 40 (76%), child development or disability services 20 (38%), respite services 6 (11%), psychological medicine services 7 (13%), the Department of Community Services 36 (68%) and remedial education services 16 (30%). Most children were referred to more than one service.

The birth prevalence of FAS in this study is 0.02 per 1,000 live births, which is much lower than rates reported in North America, South Africa, WA and the NT. However, this should be regarded as a minimal estimate because FAS is a complex disorder that is most frequently diagnosed between two and ten years of age. Indigenous children are likely to be under-represented in the APSU data due to their lack of access to paediatric services, hence under-diagnosis.

In WA, recent data from the Birth Defects Registry show that there has been an increase in notifications of FAS over the three-year period of the study due to increased awareness of FAS following our research activities.

In 2004, in addition to the surveillance of FAS through the APSU, we reported results from the *Survey of Health Professionals in Western Australia* (where we determined health professionals' knowledge, beliefs and practices in relation to FAS and alcohol consumption in pregnancy) and the *Study of Alcohol Consumption in Pregnancy in Australian Women* where we collated contemporary Australian data on alcohol consumption in pregnancy. We are now preparing papers and awaiting publication before disseminating the results of these studies.

Looking at Language - Twins and Singletons with Specific Language Impairment

Professor Mabel Rice, Institute for Lifespan Studies, University of Kansas, Professor Stephen Zubrick & Associate Professor Kate Taylor, Centre for Developmental Health, Curtin University of Technology and Telethon Institute of Child Health Research

The LOOKING at Language study aims to understand more about the genetic and environmental factors that influence language acquisition in twins and single born children during their toddler, preschool and school years. The study is collecting valuable evidence from a population-based sample of Western Australian families of twins and single-born children aged between one – eight years. Most, but not all children in the study will develop language as expected. During the study, we will identify children who have Specific Language Impairment (SLI). Children with SLI have normal development except for language. The rate of SLI in single born children is approximately seven percent. Currently we do not know the rate of SLI in twins.

The number of study participants is approaching 2000 and almost 1000 children and their family members have taken part in our face-to-face assessments of language and related abilities. In addition to the face-to-face assessments, families have returned more than 3000 questionnaires. The questionnaires provide us with important information about children's early experiences, health and development. As part of the study, researchers travel across the State to meet with the families, in some cases travelling as far away as Broome and Esperance.

Division of Population Sciences

WA Twin Child Health Study (WATCH)

Janice Hansen, Phyllis Alessandri, Kerryn Coleman, Nick de Klerk, Maxine Croft, Alan James, Paul Burton

The aim of the WATCH study was to collect data from families of multiples who belonged to the WA Twin Register, to examine the roles that genes and the environment play in the link between childhood asthma and atopy, and exposure to environmental tobacco smoke. Over 90% of eligible families of multiples born between 1980 and 1995 have been contacted and invited to join the WATCH study. Completed questionnaires have been received from nearly 2,500 families (57%), resulting in data from over 13,000 individuals. Using the questionnaire data, we were able to examine a number of asthma and atopy endpoints, including wheezing ever, wheezing in the last 12 months, current asthma, hay fever and eczema. They all showed greater concordancy in MZ twins compared with DZ twins, suggesting evidence of a genetic component. After adjusting for age, boys had a significantly higher prevalence of current asthma ($p=0.021$), wheezing ever ($p<0.001$) and current wheeze ($p<0.001$), when compared with girls, but showed no difference in the prevalence of hay fever, and eczema. However, our results indicate that exposure to ETS had little effect on the prevalence of asthma, hay fever and eczema, but that twins with older siblings had a higher rate of asthma than twins who were the first born in their families.

WATCH for Asthma study

Janice Hansen, Phyllis Alessandri, Kerryn Coleman, Nick de Klerk, Maxine Croft, Alan James, Paul Burton

The "WATCH for Asthma" study commenced in 2000 using a grant from the NHMRC. Its main aim was to explore the complexity of the asthma phenotype in WA twin families by collecting detailed clinical asthma phenotype data on a sample of twins born in WA between 1990 and 1995, and their families. Families, consisting of the twins, their biological parents and any of their siblings aged 7 and over, were invited to attend one of our Clinics to undergo a series of standard breathing, allergy and blood tests. We also offered a free zygosity test to families who are unsure of the zygosity of their twins.

Two hundred and thirty nine families, comprising 1040 individuals, have completed testing at our clinics at PMH, Busselton, Geraldton, Merredin, Northam, Bunbury and Albany. Data collection has been completed, and we are now in the process of analyzing the large amount of data that has been collected.

Newborn Encephalopathy (NE) Study

N Badawi (The Children's Hospital at Westmead, N.S.W.), JJ Kurinczuk (Oxford University, UK), PA FJ Stanley, S Silburn, SR Zubrick, JM Keogh (Hornsby Ku-Ring-Gai Hospital, NSW), PR Burton (University of Leicester, UK), J Valentine (Princess Margaret Hospital).

We have recently conducted a study examining the predictors and outcomes of abnormal brain function (newborn encephalopathy) at birth in term infants. This study involved 276 infants with brain dysfunction (newborn encephalopathy) and 564 healthy term infants born in Western Australia between June 1993 and December 1996. Our findings to date indicate that causes of newborn encephalopathy (NE) begin before birth and contrary to popular belief, very few cases, less than 10%, are due to birth asphyxia, yet many cases end in obstetric litigation. Risk factors we have identified include a family history of seizures and neurological disease, infertility treatment, increasing maternal age, maternal thyroid disease, and severe pre-eclampsia and bleeding. Among infants born with NE, there has been a 13% mortality rate, 12% with cerebral palsy and 30% of surviving cases (without cerebral palsy) with a disability compared to 5.8% of healthy infants. Additionally our follow-up thus far has found a previously undescribed association between ADD/ADHD and NE, and autism and NE with infants being six times more likely to have an autism spectrum disorder compared with infants without NE. Based on our findings to date we expect that as these children progress through school and experience puberty, when the brain undergoes hormonal changes, they will experience more physical, cognitive and behavioural problems previously unreported in this group of children. The immediate burden to the families and society of a baby with NE is clearly enormous and survivors may require lifelong care. The information from the Newborn Encephalopathy Study will assist families, educators and health providers in planning for the long-term impact of NE on the child, the family and society.

The Raine Study

The Raine Study, conducted at the Telethon Institute takes its name from Mary Raine and the Raine Medical Research Foundation at the University of Western Australia, which is an ongoing contributor to the funding of the project. It is a multi-faceted collection of data regarding a broad range of aspects of child health and development. The Study began in the late 1980s when almost 3,000 women were enrolled at between 16 and 20 weeks in pregnancy through the antenatal booking clinics at King Edward Memorial Hospital. The children have been followed at birth, 1, 2, 3, 5, 8, 10, and now 13 years of age. The investigators remain in contact with 2,300 families and most continue to contribute to the study by completing questionnaires and attending assessments at the Institute.

In 2004, data collection included measures of physical activity, physical fitness, motor competence, nutrition, posture, joint mobility, back muscle strength, blood pressure, respiratory function, allergy, and stress responsiveness. In addition, information was collected regarding child mental health and family functioning, general health, and school achievement, and blood was collected for analyses that relate to our interest in allergic conditions and the early development of metabolic disturbances.

The Raine Study is managed jointly by the Institute, The Women and Infants' Research Foundation, and the Departments of Paediatrics and Child

Health and Medicine at the University of Western Australia. Researchers from these organisations collaborate together and with researchers from Curtin University of Technology and the University of Notre Dame to study a number of important health and developmental processes that have the potential to influence health and well-being throughout life. Specific areas of interest include: the psychosocial determinants of child health and development, growth, nutrition, the metabolic syndrome, physical activity, obesity, musculo-skeletal development, asthma and allergy, and stress responsiveness. The productivity of this group is steadily increasing with a number of publications in high-impact international journals in 2004. Other features of the year were our increasing contact with Study families through regular newsletters, competitions, and our website, and the continuing development of the Study's management structures and practices.

Raine Executive: Professor Lawrie J Beilin, AO, MD, FRCP, FRACP; Dr Garth Kendall (Executive Officer), RN, MPH, PhD; Professor Louis Landau, AO, MD, FRACP; Professor John Newnham, MBBS, FRCOG, FRANZCOG, MD, DDU, CMFM; Professor Fiona Stanley AC (Chair), FAA, FASSA, MSc, MD, FFPHM, FAFPHM, FRACP, FRACOG, Hon DSc.

Assisted Reproduction Outcomes

Admission to hospital, birth defects and other health outcomes in children born following assisted reproductive technology treatment.

M Hansen, C Bower, N de Klerk, J Kurinczuk (Oxford University), L Milne, L Colvin, B Petterson, H Leonard, S Webb (HDWA)

Analyses of hospital discharge data from our study of health outcomes in children born after assisted reproductive technologies (ART) are almost complete. We compared the odds of admission over different age periods, number of admissions, length of stay, and principal diagnoses in 2106 infants born following ART in WA between 1993 and 2000 with the remainder of spontaneously conceived children born over the same time period (n=177451). Preliminary results were reported at the Australasian Epidemiological Conference in Adelaide in October and are now being prepared for publication. Singleton infants conceived following ART were approximately 20% more likely to be admitted to hospital in the first year of life after adjusting for maternal age, parity, baby's date of birth year, preterm birth, major birth defects and private insurance cover at birth. Twin ART infants were 40% more likely than spontaneously conceived unlike-sex twins to be admitted to hospital in the first year of life after adjusting for the same factors. In the second year of life, singleton ART infants were no longer at increased risk of admission to hospital, whilst ART twins had an approximate two-fold increased risk of admission. No increased risks were seen in the third year.

A number of systematic reviews examining birth outcomes of infants conceived through ART compared with infants conceived spontaneously were published in 2004. We compared and summarised the results of these reviews, together with the results of our own systematic review of birth defects following ART treatment, and presented an overview of ART birth outcomes at an IVF practitioner's conference in Adelaide in October 2004. Singleton ART infants were found to have two-fold increases in risk of perinatal mortality, low birth weight and preterm birth, about a 50% increase in small for gestational age and a 30-35% increase in birth defects compared with singletons conceived spontaneously. Few differences were observed between ART twins and those conceived spontaneously. This overview was published in the February 2005 issue of *Reproduction, Fertility and Development* whilst our systematic review of birth defects was published in the February 2005 issue of *Human Reproduction* generating nationwide media interest. The results have implications for the counselling of couples seeking ART treatment.

Other health outcomes to be assessed in this study include cerebral palsy, intellectual disability and birth defects diagnosed by 6 years of age as well as birth defects diagnosed in infants born preterm.

Intellectual disability - Hospital morbidity

Patterns of hospitalisation in children with and without intellectual disability.

Krista Williams, Helen Leonard, Edouard Tursan d'Espaignet, Lyn Colvin, Linda Slack-Smith, Fiona Stanley

As an indicator of health status, patterns of hospitalisation in the first five years of life were compared for children born between 1983 and 1992, with and without an intellectual disability. This analysis was made possible by a record linkage between the Intellectual Disability Database (now known as the IDEA Database) and the Maternal Health Research Database.

The majority both of those with mild-moderate intellectual disability and of those with severe intellectual disability – were admitted to hospital at least once in the first five years of life. This compared with less than half of children who do not have intellectual disability. Children with a medical cause for their intellectual disability or who had severe intellectual disability of unknown cause generally had more admissions. On the other hand those who had autistic spectrum disorders associated with intellectual disability had fewer.

As well as being more likely to be admitted, children with intellectual disability were more likely to stay in hospital longer if admitted. The exception to this was children with autistic spectrum disorder whose pattern was more like that of children without intellectual disability. Infections were the most frequent reason for hospitalisation both in children with and without intellectual disability. However compared to children without intellectual disability, children with intellectual disability were more likely to be admitted because of infections, respiratory and gastro-intestinal disease.

Although such information is essential to allow for appropriate planning of health

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service needs, there are few population-based data about the health status of children and adults with intellectual disability. There has been a universal trend away from the provision of specific clinical services for these children. Yet our results clearly show that children with intellectual disability have substantial medical needs that lead to a higher risk of hospitalisation for a variety of reasons in the first five years of their life. These admissions and their repercussions most likely impact not only on the children themselves but also on the rest of their immediate and extended families.

Maternal health in pregnancy and intellectual disability in the offspring: a population-based study

H. Leonard , N. de Klerk , J. Bourke, C.Bower

This study investigated the relationship between common maternal conditions and intellectual disability (ID) of unknown cause in the offspring. In at least half the children with ID, particularly those with mild or moderate ID, there is no known cause, although the factors affecting neurodevelopmental outcome are likely to be multifaceted.
Information about the maternal health of children born in WA between 1983 and 1992, both with and without ID, was obtained using record linkage. The IDEA (Intellectual Disability Exploring Answers) database was used to obtain information on the 2865 children with ID. For mothers with specific medical conditions the proportions of children with mild to moderate ID (n=2462), severe ID (n=212) and autism spectrum disorder (ASD) with ID (n=191) were compared with those who did not have ID. The comparison group were children without ID (n= 236,964) born in WA between 1983 and 1992.

For this study we selected the most common medical conditions that were present prior to pregnancy (those that were recorded in at least 500 pregnancies over the study period) as shown in Table 1 with the corresponding number of pregnancies with that condition. At least one condition was recorded for 30,970 pregnancies (12.9%) and two conditions were recorded for 4017 (1.7%). The number of pregnancies with conditions recorded increased from 7.5% (1696/22713) in 1983 to 18.5% (4623/25025) in 1992.

There was an increased risk of mild to moderate ID, varying from one and a half times to three and a half times, in children of mothers with asthma, diabetes, a renal or urinary condition and epilepsy. ASD risk was increased nearly threefold for children of women with diabetes and four and a half times for epilepsy. For anaemia, there was a fivefold increased risk for severe ID.

Although in terms of ID the population attributable risks we have identified are comparatively low, this information is still important for women affected by these particular conditions and for those involved in their clinical management. These findings are particularly important for disadvantaged or ethnic populations where these conditions are more prevalent and may be less well managed, particularly in the context of the increasing prevalence of some of these conditions, such as asthma and diabetes.

Asthma	7751	Anaemia	1101
Diabetes	2686	General herpes	929
Undiagnosed cardiac mumur	1379	Infertility	735
Hypertension	1379	Hepatitis	709
Epiliepsy	1151	Hypothyroidism	579
Renal or urinary condition	1135		

Table 1: Frequency of maternal conditions for birthd 1983 - 1992

The co-occurrence of birth defects and intellectual handicap

B. Petterson, J. Bourke, H. Leonard, P. Jacoby, C. Bower

There are few accurate assessments using population-based data of the risk of intellectual disability (ID) in children with birth defects overall or within specific birth defect categories. This study used population-based databases to ascertain birth defects and ID in children born in WA 1980-99. The WA Maternal and Child Health Research Database provided demographic, maternal and infant information and mortality data on all children born during the study period and linkage to the Intellectual Disability (IDEA) database and Birth Defects Registry allowed analysis of co-occurrence.

Of those surviving to 1 year (N=474285), 4.9 % had birth defect/s and 1.3% ID. Intellectual disability was identified in 7.9% of children with birth defect/s – giving a Prevalence Ratio (PR) of 8.3. Those with chromosomal anomalies comprised 3.2% of the group with birth defects. The % ID and (PR) in specific categories were: Down Syndrome 97% (102.6), sex chromosome anomalies 30.3% (32.1), remainder 64.2% (67.9). Birth defects were categorised according to system in the 96.8% of children with no chromosomal anomalies and the corresponding % with ID and (PR) were nervous 38.6% (40.8); spina bifida 10.8% (19.8); cardiac 4.2% (4.4); gastro-intestinal 2.2% (2.3); urogenital 2.6% (2.8); musculo-skeletal 3.6% (3.8); other 7.0% (7.4); and

multiple systems 12.3% (13.0). Adjusting for sex, mother's age, race, parity, plurality, birth weight and gestational age had little effect on the prevalence ratios.

Rett Syndrome

National - Rett syndrome: determinants of outcome and burden

Dr Helen Leonard; Professor Carol Bower; Professor Nicholas deKlerk; Professor Sven Silburn; Professor John Christodoulou; Dr Carolyn Ellaway; Associate Professor Susan Fyfe; Ms Sonj Hall; Professor Michael Msall; Dr Lakshmi Nagarajan; Professor Sheena Reilly; Dr Helen Woodhead.

The Australian Rett Syndrome study, or AussieRett as it is now known, is a population-based study following over a five-year period a cohort of Australian Rett syndrome cases born since 1976. The study aims to describe the natural history of Rett syndrome and assess the impact of the condition on resource utilisation as well as to examine the economic and social burden for families and the community.

Questionnaires are administered to families on enrolment to the study and then every two years. Information is collected on functional ability in daily living, behaviour, hand function, medical conditions, and use of health and education services. The questionnaire administered in 2004 also sought information on health and other costs and on resource utilisation. Genetic and clinical data are also collected as part of the project. The latter include clinical assessments, EEGs, ECGs, and bone densitometry.

Another important and innovative source of data for this study is video footage provided by the participants families. During 2004 considerable progress was made in the development of protocols and collection of this material. Early in the year an instruction protocol for parents to follow when filming their child was finalised, as was a demonstration video to illustrate to them what would be required. During the second half of 2004 these protocols, the demonstration video and a functional ability checklist were mailed to participating study families. By year-end 2004, 102 videos had already been returned to the study with some further returns anticipated in the next couple of months. Concurrent with the data collection a video scoring system has been developed and refined with physiotherapy, speech therapy and psychology input.

International - InterRett

Helen Leonard, Hannah Moore, Neil Leonard, Nicholas De Klerk, Sue Fyfe, David Ravine

InterRett is a five-year project, which aims to establish and manage an international phenotype database for Rett syndrome. At the end of February 2005, InterRett had collected data from 158 clinicians and 286 families from over 20 different countries around the world including the USA, UK, Spain, Argentina, China, Israel, Malta, Turkey, Belgium, Norway, India and Mexico.

Data collected are subsequently available in an innovative, interactive, user-friendly output database, available on the InterRett website (www.ichr.uwa.edu.au/rett/irsa) as shown below.

The output database contains information from questionnaires completed by participants in the form of 36 different items. These items include such areas as demographics, early development, presence of medical conditions, current functioning, hand use, presence of Rett syndrome characteristics and details of *MECP2* mutations such as the name of the amino acid change, the type of mutation and the domain of *MECP2* in which the mutation is located. InterRett cases are only included in this database if they meet the inclusion criteria. Currently the criteria for inclusion into the output database requires either a definite diagnosis of Rett syndrome by the child's managing clinician or the identification of a known pathogenic mutation in the *MECP2* gene.

This database will be marketed as a resource tool for parents, clinicians and researchers worldwide and a basis for future clinical trials and it will provide baseline data to evaluate the history of treatments. The large case numbers will greatly facilitate the analysis of phenotype and genotype correlations. It also serves as a model for the study of other rare diseases.

Down syndrome

The health, functioning and needs of children and young adults with Down syndrome in 2004.

Dr Helen Leonard; Professor Carol Bower; Professor Nicholas deKlerk; Professor Sven Silburn; Associate Professor Susan Fyfe; Ms Sonj Hall; Professor Michael Msall.

Down syndrome is the most common known cause of intellectual disability, affecting 14-15% of people with intellectual disability in Western Australia. Over the last 20 years, there has been a significant improvement in survival and life expectancy of infants born with Down syndrome, resulting in an increased demand for medical and support services. However, there has been little research investigating longitudinal changes in the health, functioning and needs of individuals with Down syndrome from childhood to adulthood, or comparing cross-sectional differences in these parameters in children of the same age born in different time periods. Such information is important for support agencies, medical service providers, educational services, and families caring for children and adults with Down syndrome, and early intervention programs. It is also of value to prospective parents considering prenatal diagnosis. Furthermore it can also make an important contribution to various areas of policy and service planning by government agencies such as WA's Disability Services Commission, for example in the long-term forecasting of accommodation needs.

The aims of the Down Syndrome Needs Opinions Wishes Study (the Down Syndrome NOW study) are to document the current health, functioning, needs (including psychosocial, employment, and accommodation needs), and behavioural

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features of children and young adults with Down syndrome; to track changes in health, functioning and needs of these children and young people over time; and to estimate the social and economic burden of Down syndrome on affected families and the community.

This study is both a follow-up and extension of a study that surveyed the parents of school-aged children with Down syndrome in 1997. The present study also involves pre-school children as well as those who have left school in the last seven years. Particular issues which are being examined which were not included in the previous study are: the psychosocial impact on families and financial costs associated with caring for a child with Down syndrome; the impact of having Down syndrome on friendships and participation in social activities, and the impact of leaving school on these friendships; the employment and accommodation needs of young people with Down syndrome; and the prevalence of autistic behaviours in children and young adults with Down syndrome and the presence of other difficult behaviours in Down syndrome, which may relate to other outcomes such as employment and accommodation needs.
During 2004, the study questionnaire was developed with input from a range of stakeholders including the Down Syndrome Association of WA and Disability Services Commission. It was subsequently mailed out to all families of children with Down syndrome born since 1980. Families have the option of completing it on paper or online. Data collection and data entry were still underway at the end of December 2004.

Child Nutrition and Growth

Childhood illness and development - Nutrition and mental health

Fatty Acids and Depression Project

Dr Wendy Oddy- Chief Investigator, Dr Garth Kendall, Professor Sven Silburn, Professor Stephen Zubrick, Assoc Professor Eve Blair, Ms Margaret Miller

The principal aim of the proposed project is to investigate the potential role of dietary and nutritional factors in modulating the risk and severity of depression and other mental health problems as measured in 2617 adolescents at 13 years of age. The study will allow for the development and testing of pilot health promotion intervention research for the testing of simple health messages related to lifestyle and depression. The specific objectives of the project are to study associations between psychosocial morbidity outcomes from birth to 13 years of age and: dietary factors (omega-6:omega-3 fatty acids, anti-oxidant intake and other; early infant feeding) and other lifestyle factors; to collect a subset of fasting venous blood samples, analyse them for fatty acids and associate these measures with mental health status including depression

Childhood Growth and Development Study

Childhood Obesity

Dr Sue Byrne- Chief Investigator, Dr Elizabeth Davis, Assoc Professor Eve Blair, Professor Stephen Zubrick, Assoc Professor Tim Jones, Professor Sven Silburn

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

Assessments include the collection of height and weight data, and measures of a broad range of biological, psychological and social/environmental factors that are purported to influence the persistence of childhood obesity into adolescence and adulthood.

Core studies for MCHRDB

Proportion of Optimal Birth Weight

Assoc Prof Eve Blair – Chief Investigator, Dr Xingyin Liu, Professor Nicholas deKlerk Dr David Lawrence

This project sought to obtain a measure of the appropriateness of intrauterine growth that adjusts for non-pathological determinants of growth and also avoids the problems of the variable burden of perinatal disease between populations and those inherent in the use of percentiles, which are shortcomings of currently popular methods of assessing intrauterine growth.

From the total population of WA births 1998-2002, singleton, Caucasian, neonatal survivors without birth defects were selected that had not been exposed to pathological factors affecting intrauterine growth, including the most prevalent of these factors, maternal smoking and hypertensive diseases of pregnancy. The intrauterine growth of these selected neonates is considered optimal. Using statistical modelling, equations for optimal birth weight, length and head circumference were obtained by considering gestational age, infant gender, maternal height, age and parity as non-pathological determinants of growth. Appropriateness of growth is assessed from the ratio of the observed birth dimension to the optimal dimension of a neonate with the same values of the non-pathological determinants of growth. This project has been documented and a revised version is being considered for publication by BMC Paediatrics.

Databases and Information Technology for Population Studies

Record linkage and the Maternal and Child Health Research Database

Peter Cosgrove, Margaret Wood, Melinda Berinson, Hoan Nguyen, Ngio Murigu, Gillian Smith.

This year saw a major step forward in the capability and value for research and policy of linked data in WA. The world famous Maternal and Child Health Research Database became an integral part of the WA Data Linkage System. This System is governed by best practice privacy-sensitive protocols that have been developed in WA and are designed to optimise linkage efficiency with minimum risk for individual privacy. ICHR now shares staff with the Data Linkage Unit (DLU) and is represented on the DLU's Executive and Management Committees. These changes will make our research data much more up to date while at the same time maximizing confidentiality of the data sources.

With the rapidly increasing amount of research data maintained at ICHR, we have developed more uniform methods for database storage, management, and cleaning, and have also started to implement an overall knowledge and information management system.

WA Register for Autism Spectrum Disorders

Emma Glasson, Glenys Dixon, Carol Bower, John Wray

Autism spectrum disorders include all autism-related conditions described medically as Pervasive Developmental Disorders. These are: Autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Autism spectrum disorders are characterised clinically by significant impairment in three areas of development: a) poor social interaction; b) deficits in communication; and c) restricted range of interests. Symptoms may be apparent before 30 months of age, but diagnosis is tentative before this time. Many children have difficulties integrating into society (eg in school, social gatherings and sporting activities), and each require varying degrees of supervision and support in daily living. Current understanding of the aetiology and intervention strategies for autism spectrum disorders is limited. The WA Autism Register serves as a primary resource to researchers, clinicians and service providers to assist with our knowledge of these complex disorders.

Since January 1999, the WA Register for Autism Spectrum Disorders has collected diagnostic information on all newly diagnosed cases in WA. The Register collects information that is useful in describing the pattern of autism diagnoses in WA, including: the number and ages of people diagnosed; the severity of disability; and shared biological, psychiatric and developmental features. Between 1999 and 2003, the Register collected diagnostic and demographic information for 980 children, adolescents and some adults who were newly diagnosed with an autism spectrum disorder.

WA Family Connections Project

Emma Glasson, Lisa Nielsen, Matthew Johnston, Nick de Klerk

The WA Family Connections Project is a newly developed resource to support genetic and familial research. The aim of the project is to create and store electronic links between genealogically related individuals as defined on birth, death and marriage registrations. The project is coordinated through the WA Data Linkage Unit, where individuals from the three types of registrations are linked using the protocols and procedures developed for the WA Data Linkage System, which are regarded as a best practice standard. The privacy-sensitive protocols were designed to maximise linkage efficiency and minimise the risk to individual privacy, while providing access to information for approved research projects. All requests for research extracts using linked data must satisfy the stringent requirements of the WA Data Linkage Unit access policies.

Phase 1 of the project has been to identify genealogical links from all available electronic registrations (n = 1,114,000 records). These exist from 1974 for births, and 1984 for deaths and marriages. Phase 2 will entail encoding genealogical links from birth, death and marriage registrations that are currently held as paper records. Phase 3 will incorporate a public appeal to improve the completeness of the Family Connections database.

ARC Linkage Grant

Stanley, F[1]., de Klerk, N[1]., Bower, C[1]., Li, J[1]., Ferrante, A[2]., Leonard, H[1]., Kendall, G[1]., Cook, J[3]., Smith, M[4]., Mathews, R[5]., Krazlan, K[6]., Vicary, D[5]., Patterson, Y[5]., Chalmers, R[7]., Freemantle, J[1].
[1]Telethon Institute for Child Health Research, UWA; [2]Crime Research Centre, UWA; [3]Department of Education and Training; [4]Department of Health Western Australia; [5]Department for Community Development; [6]Department of Justice; [7]Disability Services Commission WA

The ARC Linkage Grant was awarded in July 2004. This Grant brought together a number of Industry Partners in Western Australia. The Linkage Grant will suport the ARC Linkage Project, which is an innovative collaboration between the University of Western Australia (Centre for Child Health Research at Telethon Institute for Child Health Research and Crime Research Centre) and six government jurisdictions in Western Australia (the Departments of Health, Education and Training, Community Development and Justice, Disability Services Commission and Office of Youth Affairs). The primary aims of this collaboration are:

1. To pioneer an extensive population-level data linkage across multiple disciplines and government sectors;
2. To use this unique longitudinal data source to provide an overview of temporal, regional, socioeconomic and racial differences in developmental outcomes and to describe key risk and protective factors;

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3. To identify pathways to health and wellbeing, education and juvenile delinquency outcomes among Western Australian children and youth including those who have had contact with the Child Protection System;
4. To identify risk and protective factors for persistent juvenile offending;
5. To explore and define risk and resilience factors for Aboriginal juvenile delinquency;
6. To identify risk and protective factors for those who enter the Child Protection System and determinants of adverse outcomes after leaving the system, with a separate component for Aboriginal children.

National Cerebral Palsy register

In 2004, the Western Australian Cerebral Palsy Register continued to monitor and ascertain cases of cerebral palsy in Western Australia. Throughout the year the staff associated with the Register have co-ordinated planning for the Australian Cerebral Palsy Register (ACPR), which will ascertain all cerebral palsy within Australia. Representatives in Northern Territory, Tasmania and ACT are exploring strategies for establishing cerebral palsy registers either independently or with neighbouring States. The New South Wales Cerebral Palsy register was launched in June 2004 and the web-based software to be used for ACPR was donated to the NSW Register at the launch by Sargent's Pies and Polymorphik Software Design. In July 2004, the Queensland State government confirmed funding to establish and maintain the Queensland Cerebral Palsy Register, bringing national coverage to approximately 95%. Collaboration work has been progressing on the minimal data set for the ACPR and a classification meeting of key stakeholders was held in November to discuss further the classification processes and definitions. Funding for the ACPR has been sought through competitive research grants to enhance the ongoing notifications at a national level.

Data collection for the case control study of term and preterm cerebral palsy and perinatal deaths has been completed. Scanning by data entry did not prove satisfactory and traditional double entry computerisation was used instead. The complex relational databases are being created with Filemaker Pro and cleaned.

WA Twin Register

Janice Hansen, Phyllis Alessandri, Kerryn Coleman, Nick de Klerk, Maxine Croft, Alan James, Paul Burton.

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

The Register has since been extended to include 1993-1997 births, using part of a grant from the National Health and Medical Research Council (NHMRC) for the "WATCH for Asthma" (WFA) study (see above). A total of 11,188 multiple birth children, born in WA between 1980 and 1997 inclusive, have been identified, representing 2.5% of all births during that time.

They comprised 5,340 sets of twins, 164 sets of triplets, quadruplets and quintuplets. Forty-eight families had two sets of multiples during the time period.

Biostatistics and genetic epidemiology

Nick de Klerk, Marty Firth, Jan Hansen, Peter Jacoby, Catherine Liu.

This group has continued to work closely with all divisions within ICHR as well as our close collaborators in UWA Schools - SPACH, SPH, and SPARHC, as well as at teaching hospitals, in particular in areas involving the analysis of complex longitudinal data and survival analysis. A major part of our work now involves the analysis of genetic data from microarray experiments as well as other aspects of bioinformatics.

IDEA (Intellectual Disability Exploring Answers) Database

H. Leonard, B. Petterson, J. Bourke, C. Bower, C. Philippe, T. Schiavello

The IDEA database provides population-based information on intellectual disability in WA data based on medical and demographic information collected by the Disability Services Commission since 1953. These data have been enhanced by the addition of information provided by the Department of Education and Training on children registered with an intellectual disability in 1999 and 2002. Provision for ongoing collection of data from both sources makes the database a unique tool for providing population-based information on intellectual disability in WA. Research studies based on information from the database include a detailed assessment of the prevalence of intellectual disability in this state, socio-demographic correlates, hospital use, changes in the survival patterns, maternal health in pregnancy, co-occurrence of mental health disorders and co-occurrence of birth defects in this population.

The IDEA Inaugural Report was released in December 2004 and is available on the Institute website through the December News archives.

Advisory Council 2004: B. Petterson, C.Bower, H. Leonard (TICHR), J. Valentine (PMH), V. Morgan (UWA), R. Sanders (Dept of Education and Training), A. Rassau (DSC) R. Chalmers (DSC), P. Chauvel (Consulatant), J. Wray (SCDC), C. Rook (Consumer)

Social determinants of intellectual disability

Helen Leonard, Beverly Petterson, Nicholas De Klerk, Stephen R. Zubrick, Emma Glasson, Richard Sanders, Carol Bower

The relationship between parental sociodemographic characteristics of the mother and the presence or otherwise of intellectual disability in the child is not well

understood in Australia or elsewhere. We used the Intellectual Disability Database (now known as the IDEA Database) and the Maternal Health Research Database to investigate this in Western Australian children born between 1983 and 1992. Children with intellectual disability where the cause was not known were separated into three groups; those who had intellectual disability associated with autism, those whose intellectual disability was mild or moderate and those whose intellectual disability was severe. We found that there was an increased risk of mild to moderate intellectual disability for children of Indigenous, single and teenage mothers. We also found that compared with mothers living in those areas classified as most advantaged, those who were living in areas classified as least disadvantaged had more than five times the risk of having an intellectual disability.

The results of this study have important policy implications both in further understanding the causes of intellectual disability and in ensuring that services are most appropriately targeted for these children and their families.

Childhood Cancer Epidemiology

Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (AUS-ALL)

E Milne, C Bower, N de Klerk, U Kees, Helen Bailey, Laila Robertson, Derry Houston, Tracy Comito, Melinda Berinson, Fiona Salter in collaboration with B Armstrong (University of Sydney), F van Bockxmeer (Haematology, Royal Perth Hospital), D Baker (Princess Margaret Hospital), L Fritschi (Department of Public Health, University of Western Australia), J Thompson (WA Cancer Registry), L Lockwood (Royal Children's Hospital, Brisbane), M Rice (Women's and Children's Hospital, Adelaide), M Stevens (Children's Hospital Westmead, Sydney), E Smibert (Royal Children's Hospital, Melbourne), R Suppiah (Mater Children's Hospital), F Alvaro (John Hunter Hospital), P Downie (Monash Medical Centre), M Haber, M Norris (Children's Cancer Institute Australia for Medical Research), R Scott (Hunter Area Pathology Service), J Attia (University of Newcastle), G Marshall (Sydney Children's Hospital), M Miller (Marg Miller Consulting).

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

Case subjects comprise 350 children (0-14 years) newly diagnosed with ALL in Australia between 2003 and 2006. They are identified through all the paediatric oncology centres in Australia. Two controls are selected for each case, frequency matched by age, gender and State of residence, a total of 700. Controls are identified using random digit dialling. Data collection instruments were specifically developed for use in the study: self-administered exposure questionnaires for each parent and food frequency questionnaires for the mother (during pregnancy and breastfeeding), the father (in the 12 months prior to the pregnancy), the child's current diet (completed by the parent) and their diet as an infant. Telephone follow-up interviews ask about occupational and other exposures. An occupational exposure expert, blinded to case/control status, will examine all the occupational information and allocate probability and amount of exposure to the chemicals with reference to a custom designed database of jobs and exposures.

Blood and buccal samples are taken from the case child (in remission), and blood samples are taken from his/her parents. Buccal samples are being collected from the first 350 control children and their parents. Genomic DNA is isolated by standard techniques, and polymorphisms in specific folate metabolizing enzymes, xenobiotic metabolising enzymes and DNA repair enzymes are to be examined. The main effects of genetic and environmental factors, and the biological interactions between them, are to be quantified in this study.

The study is well under way. To date, 237 cases have been notified to us, 205 (86%) of whom have achieved remission and are thus eligible to participate. Approximately 99% of children go into remission, so the rest will become eligible in the near future. 184 of the cases in remission have been invited to participate, of whom 144 (78%) have consented, 20 have yet to consent, 18 (10%) have declined and 2 died before consent was given. DNA collection is complete for 108 (75%) recruited cases, and 95 (66%) case families have completed questionnaires. To date, 400 (60%) recruited control families have completed exposure questionnaires, and 327 (49%) have provided DNA samples. Genotyping for MTHFR polymorphisms has been completed in more than 100 DNA samples.

The interaction between folate and folate metabolising gene polymorphisms and the risk of childhood Acute Lymphoblastic Leukaemia

E Milne, N de Klerk, U Kees, in collaboration with B Armstrong (The University of Sydney), F van Bockxmeer (Biochemistry, Royal Perth Hospital), D Baker (Princess Margaret Hospital), J Thompson (WA Cancer Registry)

We have previously shown a protective effect of maternal folate supplementation during pregnancy on risk of acute lymphoblastic leukaemia in children, and a number of studies have reported a protective effect of some common polymorphisms of the methylenetetrahydro-folate reductase

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(MTHFR) gene. Other studies have suggested that the effect of *MTHFR* polymorphisms on risk may depend on folate status. This study aimed to look for evidence of an interaction between maternal folate supplementation and child's genotype among the cases from our earlier study.

Bone marrow specimens from 82 case children from the previous study were available. DNA was extracted and genotyping for *MTHFR C677T* and *A1298C* undertaken using standard techniques. We used a case-only analysis to estimate the case-only odds ratio (COR) between *MTHFR* genotype and folate supplementation associated with ALL. None of the CORs indicated a significant departure from a multiplicative model. Adjustment for sex, age or genotype at the other locus made little difference to the results. A manuscript describing the findings is in preparation.

Success of buccal DNA collection using buccal swabs compared with FTA(R) cards.

E Milne, U Kees, H Bailey, L Robertson in collaboration with B Armstrong (The University of Sydney), F van Bockxmeer and J Brisbane (Biochemistry, Royal Perth Hospital), L Ashton (Children's Cancer Institute Australia).

This methodological substudy set within AUS-ALL aimed to compare the effectiveness of DNA collection by two methods suitable for use in children. DNA was collected from 115 children using both methods, and the proportion of successful collections compared. PCR was successful using DNA from buccal swabs from 80.9% of children, and from the FTA(R) card in 92.2% of children. However, the difficulty involved in handling the disks needs to be taken into account when planning data collection and processing methods. Our research team is currently looking at ways of minimizing the problems involved in handling the FTA(R) discs; a manuscript is in preparation.

Social, Economic and Psychological and Cultural Determinants of Health

Modern society and children's well-being

Completed a theoretical paper that explains the modernity's paradox (unprecedented economic prosperity but increasing poor child outcomes) from sociological, demographic, economic and cultural perspectives. The paper has identified a number of new areas of social determinants that are important for child health research. The paper will be submitted in May 2005 to a high quality international journal for publication.

Health-related behaviour as a mediating factor underpinning socioeconomic inequality in health

Completed a first author and an empirical paper on the influence of maternal psychosocial wellbeing on breastfeeding duration. This is a collaborative study between Jianghong Li, Saras Henderson, Wendy Oddy, Garth Kendall, Jill Downie and Linda Landsborough. The paper was presented at Australasian Epidemiological Association Annual Conference, Adelaide, 11-12 October 2004. The results show strong socioeconomic and demographic gradients in breastfeeding duration. That is older, better-educated mothers and mothers who have entered a marital relationship tend to breast their infants for a longer duration than younger and less well-educated mothers and mothers who are never married or in a defector relationship with their partners. These social gradients are linked to the larger picture of social inequality of health well documented in the literature. Inadequate breastfeeding, as a behavioural risk factor, is an important mechanism that underlies poor health and developmental outcomes in children from social and economically disadvantaged parents. The findings also demonstrate that lack of social contact and support, having 3 or more stressful life events and sustained emotional upsets throughout pregnancy and the intensity of "baby blues" accelerate the cessation of breastfeeding. These findings suggest that not only support for breastfeeding per se, as shown in previous research, but also wider social support and maternal psychological wellbeing are important factors. The findings suggest that these social and psychological factors are some of the barriers to achieving adequate breastfeeding in socially disadvantaged mothers.

Children from other culturally and linguistically diverse backgrounds

This area of work has two focuses. One is on the impact of cultural, social (discrimination) and language barriers on mental health (including suicide) and school achievement in children from culturally and linguistically diverse backgrounds (CALD). Working together with Kristine Ward, Sven Silburn and Steve Zubrick, Jianghong Li has identified a number of projects that will address these issues. The other focus is on culturally sensitive approaches to identity CALD children at risk and the inappropriateness of the application of universal diagnostic and screening tools based on dominant culture to CALD children. Together with Dr Amedeo D'Angiulli from University College of Cariboo and University of British Columbia, Canada, Jianghong Li has completed a paper on the EDI. The paper has identified both the strengths and weaknesses of the EDI as a universal screen tool, particularly with regard to children from culturally and linguistically diverse backgrounds, and has made recommendations for modifications.

Biopsychosocial pathways to healthy child development

Dr Garth Kendall is recently completed his PhD thesis and leads the effort to document the coacting personal and contextual factors associated with developmental health outcomes, latency and pathway effects of family life-stress on mental health in childhood, and the investigation of trajectories of developmental comorbidity. Dr Kendall currently leads a research group that is funded through a NHMRC Program Grant (Stanley et al, 2005, #353514) to

collect Raine Study data at 16 years to: 1) describe the mental health trajectories from age two to 16 years; 2) quantify the degree to which the mental health trajectories are predictable on the basis of lifetime biopsychosocial characteristics; 3) assess and quantify which combinations of biological, psychological, and social characteristics operating in this developmental epoch are most likely to result in adverse mental health trajectories; and 4) quantify the extent to which timing and accumulated burden are both important determinants of risk impact.

Dr Kendall is a member of the New Investigators Network for Human Development, a part of the prestigious Canadian Institute for Advanced Research and he is personally mentored by Dr Clyde Hertzman at the University of British Columbia. He is an investigator on a Canadian project with Dr Doug Willms and others entitled "Raising and leveling the learning bar". Dr Kendall is collaborating on a number of papers with his Canadian colleagues, using a novel person-centred analytical strategy he has developed. He has been appointed to the Australian steering committee of "Roots of Empathy", a school based program designed in Canada to enhance children's emotional and social competence, and academic achievement and he is coordinating the evaluation of a pilot of the program in Western Australia. Dr Kendall also teaches a postgraduate unit in Developmental Health at the School of Nursing and Midwifery at Curtin University of Technology and he is involved in a number of research projects and student supervision with his nursing colleagues.

Postdoctoral fellowship: Mailman School of Public Health, Columbia University in New York

Dr Eugen Mattes

Eugen Mattes, the inaugural NHMRC General Practice Fellow, is currently undertaking a two- year postdoctoral fellowship at the Mailman School of Public Health at Columbia University in New York City. He is affiliated with the prestigious Health and Society Scholars Program at Columbia University funded by the Robert Wood Johnson Foundation. One of the main features of his fellowship is to examine some of the cutting edge theories and methods required to investigate the social determinants of health especially related to the health and development of children. Dr Mattes is collaborating with Professor Ezra Susser and his team from the Mailman School of Public Health at Columbia University, and he has contributed to the submission of a grant application for Columbia University and its affiliated institutions to become a Vanguard Centre in the one billion dollar National Children's Study in the United States. This Study is due to commence in 2006.

Chicago Neighborhoods Study - He is also collaborating with Professor Jeanne Brooks-Gunn on research that examines the social determinants of health, specifically focusing on the effect of social institutions on child development in the landmark Chicago Neighborhoods Study.

Social environments and their impact on neurobiological pathways in children - Dr Mattes and Dr Kendall are collaborating with Dr Anke van Eekelen and Associate Professor Jonathan Foster to examine the neurobiological pathways through which the social determinants operate. Specifically, they are investigating in the Raine Study how early life stress influences adolescent HPA functioning and perturbs neurodevelopmental processes during adolescence aimed at remodelling corticolimbic neural networks, which underlie cognition and emotion.

Adolescent Development

Virtual Parenting Project

The Virtual Infant Parenting (VIP) program is a school based health promotion program, which aims to reduce adverse maternal and child health outcomes associated with unplanned teenage pregnancy and parenthood. Healthway and LotteriesWest are funding the implementation and evaluation of the VIP program. The program was developed with the North Metropolitan Area Health Service in partnership with the Osborne and Perth Central Coastal Divisions of General Practice.

All government and independent schools in the North Metropolitan Area Health Service region were invited to participate in the VIP program.
The program is being offered to 2,000 year nine and ten female high school students during 2003 to 2005.

The VIP program is implemented by Community Nurses in conjunction with General Practitioners. The program content covers health issues affecting infant and maternal health, such as smoking, nutrition, alcohol and other drugs, physical activity and support systems. A key component of the program is for the students to care for an infant simulator over a weekend period. The infant simulator replicates the sleeping and feeding patterns of a 6-week-old infant.

Teenage Pregnancies

Dr Rachel Skinner, Honorary Research Associate, Division of Population Sciences

Prospective study to determine the efficacy and acceptability of etonogestrel contraceptive implants (Implanon) in an adolescent postnatal population (Skinner, Hickey, Doherty),
Funding is from the Women's and Infants Research Foundation, Raine Medical Research Foundation $127,477). 160 adolescent females are being recruited through the King Edward Memorial Hospital's adolescent antenatal clinic and followed over a two-year period. In the postnatal period participants will be offered contraceptive and sexual health counselling and contraceptive options. Participants are followed for 2-years with 4 home visits and 4 telephone interviews. Data is being collected at these times for contraceptive acceptability (using

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standardised questionnaires), side effects, continuation, repeat pregnancy, condom use and STD. Study outcomes include percentage uptake of Implanon, contraceptive acceptability, incidence of side effects, incidence of pregnancy, frequency of condom use and incidence of chlamydia and gonorrhoea infections between Implanon users and users of other forms of hormonal contraception.

Why do so many teenagers fall pregnant? Exploring the bio-psychosocial antecedents of repeat teenage pregnancy

Skinner R., Hickey M., Doherty D.

This study is being run in parallel with the teenage Implanon cohort study, with the same sample of teenage mothers. This study aims to evaluate the factors that influence the use of contraception in teenage mothers, and their likelihood for repeat pregnancy. Instruments incorporated into the questionnaires measure functioning across a broad range of bio-psychosocial factors. These instruments have been standardised and validated in a Western Australian teenage population, and data will be compared with the general population of teenagers. This data will also be linked to the Western Australian Data Linkage System to measure intergenerational teenage pregnancy patterns and outcomes.

Why do Australian teenagers fall pregnant? Exploring pathways to teenage pregnancy:

Phase 1 and 2 (Skinner, Zubrick, Hickey, Milroy, Fyfe, Kendall, Doherty)

This is a 2-stage project that seeks to: 1) reveal perceptions, values and beliefs about pregnancy and childbearing in Aboriginal and non-Aboriginal Australian teenagers; and 2) elucidate complex biological, psychological, and social pathways to unplanned pregnancy in the teenage years.

Phase 1 (2005-2006): Perceptions, values and beliefs regarding pregnancy and childbearing/pregnancy termination will be explored in a qualitative analysis in three groups of sexually active Aboriginal and non-Aboriginal teenagers: never-pregnant, pregnant-continuing and pregnant-terminating. Individual semi-structured interviews will be used to collect the data. Using a grounded theory approach, an explanatory model will be developed for each of the three groups. The models will then be compared and the similarities and dissimilarities identified, and hypotheses regarding pregnancy and childbearing risk generated.

Phase 2 (2006-2007): A cross-sectional survey of sexually active teenagers with sample enrichment of pregnant-continuing and pregnant-terminating teenagers will be undertaken and data, including questions regarding perceptions, values, and beliefs about pregnancy and parenthood developed in phase one will be collected via computerised questionnaires.
This phase seeks to:

1) Quantify the degree to which beliefs, individual, familial, and extrafamilial factors are associated with effective contraceptive use, termination, and childbearing;
2) Quantify the degree to which factors from multiple systems of influence interact or otherwise combine with each other to shape sexual and childbearing behaviour; and
3) Identify those factors, or combinations of factors, leading to teenage pregnancy that are amenable to intervention.

A study to demonstrate immunogenicity and tolerability of the quadivalent HPV (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine in pre-adolescents and adolescents and to determine end-expiry specifications for the vaccine

Richmond, Skinner, Leake, Loh

This study has recently been completed. This was an international multi-centre randomised controlled trial of safety and efficacy of an investigational HPV vaccine in an adolescent and young adult population. 50 subjects were recruited in Perth for this study.

A phase III, double-blind, randomized, controlled study to evaluate the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine administered intramuscularly according to a 0, 1, 6 month schedule in healthy female subjects aged 10 – 14 years

Skinner, Richmond, Leake, Moller, Loh

The aims of this study are to demonstrate that 3 doses of the GSK investigational HPV vaccine (containing HPV 16, 18) are safe and stimulate a protective antibody response in healthy girls aged 10 – 14 years. This is an international trial and 2,000 young teenagers will be invited to participate in the study. We have recruited 67 participants and the study is on-going.

A phase III, double-blind, randomized, controlled, multi-center study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccine as control, in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy females 15-25 years of age

Skinner, Richmond, Leake, Moller, Loh

The aims of the study are to demonstrate that 3 doses of the investigational HPV16, 18 vaccine (prevent persistent infection with these types of HPV, pre-cancerous and cancerous changes of the cervical cells, and to further evaluate the vaccine's safety. This is an international trial and 13,000 healthy young adult women (15 to 25 years of age). We have recruited 125 participants so far, for a target of 150.

Suicide Prevention

Western Australian Ministerial Council for Suicide Prevention

SR Silburn (Chair), BE Williams (Executive Officer), KM Miller, NF Mudgway, DJ Robertson, M Sayers, KA Ward.

The Institute supports a program of translational research in suicide prevention. This research aims to ensure that new knowledge on the aetiology and epidemiology of suicide and suicidal behaviour can be applied in current policy and practice. An important component of

this is the accommodation of the Ministerial Council for Suicide Prevention (MCSP) at the Institute. The MCSP reports through the Minister for Health to all other Ministers on the Cabinet Sub-committee for Social Policy and is responsible for advising government and supporting effort, across government and non-government agencies, to reduce the morbidity and mortality associated with suicide and self-harm. The MCSP is also active in advancing scientific and community understanding of suicide and its prevention. The membership of the Council includes representation of government departments concerned with social policy, non-government agencies, and key community stakeholders. This has facilitated new knowledge in suicide prevention being implemented in the policy and practice of these organisations.

The MCSP is also responsible for maintaining the WA Coroner's Database on Suicide. This is an on-going collection of epidemiological surveillance data on suicides by persons of all ages in Western Australia. It has provided some of the first Australian data delineating key risk and protective factors for suicide among young people. It is also used for the monitoring of emerging trends, such as a recently observed increase in illicit drug use associated with suicide among young people.

The MCSP coordinates a program of research into the hospital and community management of deliberate self-harm. This has included the design and maintenance of a deliberate self-harm database within each of the three adult teaching hospitals in Perth. This database has been used to monitor trends in deliberate self-harm admissions and to monitor the progress of the implementation of the practice guidelines developed by the Royal Australian and New Zealand College of Psychiatry and the Australian College of Emergency Physicians.

Funding from the Australian Government's National Suicide Prevention Strategy (NSPS) has enabled the MCSP to conduct an 18-month study regarding the prevention, treatment and support needs of suicidal males aged 17-35 years. The project commenced in December 2002 and utilised qualitative and quantitative research methods in a consumer consultation process to inform and support the development and improvement of suicide intervention and prevention initiatives in Western Australia. Consultations included consumers from the general population, at risk groups, carers and service providers, totalling 591 participants. This required the development of appropriate and responsible risk management protocol to ensure the safe and ethical collection of information from individuals who were at known high-risk. It entailed extensive interagency negotiation and cooperation and involved the back-up availability of community crisis services and generalist counselling organisations. This study has provided internationally unique data on suicidal men's knowledge, attitudes and behaviours in relation to help seeking and service and support access. Funding is now being sought to use the findings from the study to inform universally targeted media-based prevention strategies as well as initiating changes to current community based treatment services to make them more accessible and appropriate to men's needs.

The Resource and Information Strategy secured corporate funding over three years from January 2002, through a joint proposal with Woodside Energy Ltd. and the Telethon Institute for Child Health Research, to assist in the development of a national information and resource system for suicide prevention. The strategy includes dissemination of new information and targets both professionals and the community. ASPiRE (Australian Suicide Prevention information and Resource Exchange), launched in November 2002 now provides access to over 3,000 research articles and resources. ASPiRE is located on the MCSP website at www.mcsp.org.au. Another important component of this strategy is translating the research conducted by the MCSP into resources into resources and training for service providers and communities. In 2004 the publication '*Using the Internet for Suicide Prevention*' was published in 2004, based on research conducted by the MCSP. The guide seeks to assist community members and professionals in accessing safe, accurate and appropriate suicide prevention information, counselling and chat room on the Internet. Other publications including fact sheets, summary booklets and newsletters are available on the MCSP website.

The "*Information and Support Pack for those bereaved by suicide or other sudden death*" was produced by the MCSP with funding through the NSPS. The development of this key resource was informed by research on the information and support needs of families bereaved through suicide. The pack is distributed through the Coronial counselling service to all families bereaved by suicide or other sudden death. It is also available online at www.mcsp.org.au. NSPS funding has allowed for the evaluation of the pack to ascertain the usefulness and perceived relevance of the publication by its recipients. Notwithstanding the limitations of the small sample size, the summary of findings from the respondents, representing not only next of kin but also other family/friend members, indicated strong support for the publication and the need for on-going distribution of such an Information & Support Pack to those bereaved by suicide. The majority (75%) reported finding it very helpful during their bereavement.

The Education and Training Working Group delivers suicide prevention training and coordinates the Regional Trainers' Program that provides suicide prevention training across the state. In 2004 a study into the implicit theories about suicide causes, risk behaviours and prevention strategies of participants of the Gatekeeper workshop and whether or not training alters these beliefs. The study found that following training, and when compared to a group of non-trained peers, participants' implicit theories changed on a number of dimensions, including; increased endorsement of social isolation as a cause of suicide, several signs of suicidal behaviour, including preparation for dying and the benefits of proactive

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interventions and social support as suicide prevention. In 2004, over 700 people in WA attended Gatekeeper training, through the Ministerial Council for Suicide Prevention. In 2004, the regional trainer network consisted of 80 accredited and trainee Trainers.

The continuing high rates of suicide and self-harming behaviour in the Aboriginal population and some areas of WA are a major concern. The Aboriginal Suicide Prevention Steering Committee (ASPSC) reconvened on the 7th April 2004 with sound representation from the key agencies and Aboriginal organisations taking a strong leadership role. Based on the outcomes of this meeting, a new proposal for the ASPSC, detailing membership and structure, is to be finalised. In the interim, the MCSP continues to seek Aboriginal representation within its working groups and to respond to the suicide prevention needs of Aboriginal communities, particularly in education and training, with a recent appointment of Training in Aboriginal and Torres Strait Islander position.
More information is available at www.mcsp.org.au

Capacity Building Grants

Capacity Building Grant in Population Health

In 2002, researchers at the University of WA School of Population Health, in conjunction with researchers at the Institute, were awarded the first ever NHMRC Capacity Building Grant in Population Health. The lead applicants on the Grant are Professor D'Arcy Holman, Professor Fiona Stanley, Professor Steve Zubrick, Professor Nick de Klerk, Professor Matthew Knuimann, Professor Michael Hobbs, Professor Philip Weinstein and Professor Carol Bower. The overall aim of these grants is to build the capacity of promising researchers (called team investigators) in population health research. The title of our grant is "*Better health outcomes through new research methods and population data*" and the team investigators are Liz Milne, Garth Kendall, Eugen Mattes and Jianghong Li at the Institute, Delia Hendrie, Max Bulsara and James Semmens at the School of Population Health, and Emma Glasson and Anne MacKenzie across both institutions.

The overall research objective of the grant is to improve health outcomes through new research methods and biological, social and environmental data resources developed at the population level and integrated across the entire human life span, building on existing strengths in the creation of large databases for population health research. Research capacity of the team investigators is being built, using a framework of six research themes:

Theme 1: WA Family Connections Genealogical Database

Theme 2: Social and Environmental Determinants of Child Health and Biological Pathways

Theme 3: Spatial Analysis, Social Mapping and Access to Health Supports

Theme 4: New Dimensions in Childhood Cancer Epidemiology

Theme 5: Quality and Value in Health Care

Theme 6: Community Participation in Population Health Research

There has been outstanding progress in the career development of the team investigators. Their publications numbered 13 in the latter part of 2002, 52 in 2003 and 55 in 2004-5. Their profile at international and national conferences has been excellent, with 24 presentations in late 2002, 41 in 2003 and 52 in 2004-5. Also of note has been the degree of participation of the team investigators in scientific and expert advisory committees at the international, national and state levels and the new international and national collaborative networks they have forged.

Indigenous Capacity Building Grant - Not Just Scholars but Leaders: Learning Circles in Indigenous Health Research

Lead Applicants: D Lehmann[1,2], FJ Stanley[1], S Eades[3], N de Klerk[1], M Gilles[4], D Gray[2], A Larson[4], L Slack-Smith[5], S Thompson[2], C Watson[2]
Team Investigators: H Milroy, D McAullay, C Kickett-Tucker, N Brown, J Jones, ET Wilkes, M Wright, D Bessarab, J Coffin, nominated Medical Student
[1]Telethon Institute for Child Health Research, [2]Curtin University of Technology, [3]Institute for Health Research, Sydney, [4]Combined University Centre for Rural health, [5]School of Dentistry, University of Western Australia

In November 2004 we were awarded an NHMRC $2.5 million Indigenous Capacity Building Grant in Population Health Research over five years. This collaborative research proposal brings together a team of population health researchers with a team of highly talented Indigenous achievers Australia-wide, including two medical doctors and two researchers who have completed doctorates and seven with Masters degrees. There are four major themes. The first aims to *improve quality of relevant research, increase Indigenous people's participation in research and identify optimal ways of providing feedback* of research findings. The second theme will examine the *provision and use of health services* to develop a better understanding of the best and most cost-effective ways of providing preventive and acute care for Indigenous Australians. The third theme explores *lifestyle, behaviours and susceptibility to disease* and the fourth theme will investigate the factors in people's lives that influence health in a positive way - *pathways to resilience and wellbeing.*

The Applied Research Projects in Child Health

DOH Contracted Projects
The Collaboration for Applied Research and Evaluation manages a $1 million contract with the Department of Health (DoH) aimed at the provision of applied research services relevant to maternal and child health. The first half of 2004 was spent finalising projects negotiated under the 2003-2004 contract as reported in the 2003 annual report. The second half

of the year entered a new phase of the Institute's relationship with the DoH with the signing of the 2004-2007 contract. This new contract represents tangible recognition of the interconnection of research, policy and service delivery. It demonstrates the DoH's acknowledgment of the research undertaken by the Institute and the outstanding contribution this has, and continues to make to the health and wellbeing of children, adolescents and their families in Western Australia. The Institute's record of research excellence and achievement in informing policy and health care practice and service delivery in this State and nationally, makes us a valuable partner in population health initiatives to reduce preventable disease, injury, disability and premature death in the West Australian community. The ongoing collaborative partnership between the Institute and the DoH is expected to produce policy and practice relevant outcomes through the dissemination and application of information and research knowledge, and through expert advice and consultation from the State's leading researchers in child health. This partnership is aimed at providing the foundation to improving child, youth and family health and wellbeing outcomes in this State in years to come.

The 2004-2007 contract covers two areas, a 'fixed deliverables' output and a project deliverables output. The fixed deliverables output is centred around information provision and the application of the research into policy and practice. The Institute's long standing goal of effective transfer of maternal and child health research into policy has prompted the establishment of a process to better understand the pathway for the translation of policy into practice in Western Australia. It is anticipated that the Institute will facilitate a partnership working group in 2005 with the aim of bringing together key representation from each of the layers working within our complex health system to produce policy and practice relevant information that will be useful to the health system.

The project deliverables output provides funding for research projects currently undertaken by research groups at the Institute and these include the Vaccine Impact Surveillance Network, the Birth Defects Register, Family Connections Project, preliminary evaluation of the Ngunytju Tjitji Pirni Program and Hearing Screening Evaluation (HeLP). Other projects funded under this output are delivered by the Collaboration Team and these projects include evaluation of Community Mothers Program, evaluation of Mission Australia's Girradoola Pathways Project, recruitment strategy for the Virtual Infant Parenting Project, report on the development of a model for the WA Nutrition Market Basket Survey and the provision of support to Health Promotion Services.

Other projects

The Collaboration Team has also attracted funding from other agencies to undertake applied research projects including a contract with South West Area Health Service to undertake a database project called the Human Services Collaboration Project. Further, the Collaboration Team also undertook a small project to evaluate the effects of the Family Partnership Training Program as funded by the State Child Development Centre.

West Australian Population Health Training Program

As part of the West Australian Population Health Training Program, Public Health Trainee, Janine Smith completed a placement with the TICH exploring the relationship between research, policy and practice. A brief summary of her study is attached below:

Background

There is a growing body of literature on how health research can inform health policy and practice but many of the lessons learned about developing an effective interface with policy makers and practitioners have not been widely implemented. This article describes researcher's perceptions about effectively translating research knowledge into policy and practice within the Population Science Division of the Child Health Research Institute in Western Australia.

Results

Comparing the actual views and practices of participants to the practices from the literature, identified opportunities for improving how research knowledge can be translated into policy and practice. The study showed a poor understanding amongst researchers of the realities policy makers face in interpreting and applying research knowledge, whereas policy makers had a poor understanding of the research environment. Participants agreed research should be translated to decision makers but were unclear as to who they were. Participants believed that research knowledge translation is a complex web of activity occurring at multiple levels with no guiding frameworks. A continuum of approaches to research knowledge translation was used, ranging from the traditional to more innovative approaches. Innovative approaches appeared to be more successful in ensuring translation of research to policy and practice. There was little evidence to suggest knowledge translation activities are evaluated for impact and outcome.

Conclusions

The case study suggests that the greatest opportunity for translating health research to policy and practice is to involve policy makers and practitioners in the research process from the beginning. It is argued a cultural shift is required that enables researchers, policy makers and practitioners to engage and exchange ideas. Researchers, policy makers, practitioners and funding bodies need to create more opportunities for dialogue and exchange through collaborative research partnerships and the development of a framework to guide the translation research to policy and practice.

Community and Consumer participation

The Institute was awarded a NHMRC Capacity Building Grant in 2003, that enabled the shared appointment of a Consumer Research Liaison Officer between the Institute and UWA School of Population Health. Having this position

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has provided the Institute with a unique opportunity to develop plans to:

- Support the ethos of the National Health and Medical Research Council and the Consumers' Health Forum Statement on Consumer and Community Participation
- Expand and build on current consumer and community participation, in particular widen the established strengths of the Kulunga Research Network to other areas of the Western Australian community

During 2004 several events were undertaken; these included a workshop for senior staff, auditing consumer participation activities in current research projects and a consumer and community meeting.

Several common themes emerged from these activities such as: need for training for both researchers and consumers, funding and communication issues. The findings have been summarised and will be used to develop further planning to increase consumer and community participation.

During 2005 it is proposed to establish Consumer Advisory Council for the Institute, a policy on consumer and community participation and appropriate training to support both researchers and the community.

Centre for Developmental Health

The Centre for Developmental Health is a joint venture between the Telethon Institute for Child Health Research and Curtin University of Technology. Established in June 2001, this multidisciplinary centre has brought together researchers from several disciplines in child and life-course human development with the aim of improving population outcomes in health, education and social wellbeing. It is operationally based at the Institute but also conducts some of its activities on the Curtin campus in Bentley. This arrangement has enabled productive research collaborations within the Institute and other areas of Health Science at Curtin (e.g. Centre for Behaviour Change and Cancer Control, School of Psychology, School of Nursing, and the National Centre for Aboriginal Studies). Developmental health is a relatively new field of research which seeks to explain how health trajectories develop over an individual's lifetime and how this knowledge can guide new approaches to policy, practice and research. It integrates understandings from the fields of public health, the biological sciences and medicine, child development and the social sciences. Each of these fields offer useful perspectives on the ways in which health and diseases develop. Together they afford a much broader understanding of health than more traditional conceptions.

It is now evident that some of the greatest risks to the healthy development of children are created and maintained by social systems and that the magnitude of these risks is largely a function of socioeconomic disparities. This means that efforts to reduce health disparities can no longer be confined to providing better service access and more resources to address the special needs of the disadvantaged. The developmental health perspective offers a systematic means of informing action to address the underlying social, economic and other environmental factors that determine these disparities. Over the past three years the Centre has developed a national and international profile in academic research and policy areas relevant to developmental health. It has developed strong links with government and other agencies responsible for the health, education and wellbeing of children in Western Australia, and Australia. In the first three years of operation the Centre's researchers successfully competed for grants totalling almost $8 million dollars.

During 2004 the Centre supported Dr Garth Kendall in setting up Australia's first post-graduate course in developmental health through the Curtin School of Nursing and the Division of Health Sciences. The Centre's co-directors, Professor Steve Zubrick and Professor Sven Silburn, together with five other Chief Investigators at the Telethon Institute for Child Health Research were awarded an prestigious NHMRC program grant for "Studies in Child Health: Populations, Pathways and Prevention" to be conducted 2005-2009. Some $2.7 million of this funding is expected to be managed through Curtin University and will be focussed on the program themes dealing with the social, economic and psychological determinants of health; nutrition, growth and mental health; and Aboriginal health.

Staff and students

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Kulunga Network Manager

Associate Professor C Hayward. *BEd, B Sc (Community Management and Development)*

Head of Epidemiology

Professor C Bower *MBBS, MSc, PhD, FAFPHM, DLSHTM*

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K Alpers *RA*
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A Baptista *BSc Hons*
T Barker *BApp Sc*
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M Berinson *BSc Hons MPH*
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Dr S Fyfe *BSc, BEd (Hons), BAppSc (Hons)*
Dr L Gibson *BA (Hons) PhD*
Dr E Glasson *BPsych, BSc (Hons), PhD*
E Hagemann *BSc (Speech and Hearing Science) Hons*
J Hansen *MPH, BSc (Hons)*
M Hansen *BSc MPH*
C Harrison *RN*
Dr T Heaton *PhD*
S Hoey *RN*
D Houston *BA / MSocWk*
A Italiano *BPsych*
T Jackiewicz *Bsc (Hons) MPH*
S Jackiewicz *B.Soc.Sci (CS) M.Soc.Sci.*
P Jacoby *BA (Hons), MSc*
Dr R James *MA, MPH, EdD*
Dr C Jeffries-Stokes *MBBS, FRACP, MPH*
J Johnson Administration Assistant
M Johnston *BSc (Hons)*
Dr G Kendall *RN, MPH, PhD*
M Kepert *MPH, PostGradDip (HealthSci), BPsych*
Dr C Kickett-Tucker *PhD*
Dr J Kurinczuk *MSc, FFPH, FAFPHM*
C Laurvick *BA MPH*
Dr D Lawrence *BSc, PhD, ATCL*
M Ledger *BSc (Human Communication Science)*
Dr D Lehmann *MBBS, MSc*
Dr H Leonard *MBChB, DCH, MPH*
Dr J Li *BA, MS, PhD*
Dr E Mattes *FRACGP, PhD, MPH, MBBS*
D McAullay *BSc, MAE*
M McClurg *BSc, MSc (Speech Pathology)*
A McKenzie Consumer Consultant
K Miller *BSc MHP(Health Promotion)*
Dr E Milne *BAppSc (Physio), MPH, PhD*
F Mitrou *BEc*
R Monck *RN, RM*
H Monteiro *BA SocSci,*
H Moore *BSc (1st class Hons)*
K Moore *Secretarial Diploma*
N Mudgway Administrative Assistant
V Muniandy *BEd (Early Childhood)*
N Murigu *BBus*
K Murray *BSc (Human Communication Science)*
H Nguyen *BAppSci*
Dr F Nichols *PhD*
L Nielsen *BSc, GradDip PubHlth*
Dr W Oddy *BAppSci (Nutrition) MPH, Ph.D*
R Param *BSc*
D Parsons *B.Sc (Hons)*
J Payne *SRN(UKCC), P Grad Dip(Hlth Admin), MSc (Pub Hlth)*
Dr B Petterson *PhD, MSc Biochemistry, BSc (Hons) Physiology*
C Phillippe *RN*
N Pomat *Secretarial studies*
M Quail *RA*
Dr P Richmond *MRCP, FRACP*
D Robertson *BA DipEd, MPhil*
L Robertson *B.Hlth.Sc (Hons)*
A Robson *BSWk*
F Salter *BSc (Hons), Nutrition & Diabetics*
M Sayers *BSW*
E Scheepers *BA, AdvCert Tvl Cons*
P Serna *BA (Hons)*
E Seymour *MSocSc*
Professor S Silburn *BSC(Hon) MSc(ClinPsych) MAPS*
Dr D Silva *MB BS, FRACP, MPH*
Dr R Skinner *MBBS, PhD, FRACP (Paediatrics)*
N Sloan *BSc Hons*
C Smargiassi Data Entry Clerk
G Smith *BPsych, Master of Psychology (Applied Developmental), Grad.Dip.Ed*
R Spencer Aboriginal Education and Training Officer
S Steffanoni *BA*
A Stokes *Health work (Advanced Certificate), Early Childhood Certificate*
M Stone *BA(Psych), MSc(SpPath)*
Dr K Taylor *BAppSc, PGradDipHlthSc, PhD, FSPA*
M Tennant *RN, RM, BAppSc, MPH*
A Thompson *BSc CN*
Dr J Valentine *MBBS MRCP(Edin) FRACP FAFRM*
K Ward *RMHN, BAppSci (Psych), MSc (Public Health)*
A Watkins *BPsych, Post Grad.Dip. (Psych).*

Division of Population Sciences

L Watson *RA*
F Watt *B.Psych*
Dr K Watts *BSc (Hons) PhD*
Associate Professor E Wilkes *BA (Social Science)*
M Williams *RA*
A Williams *BEd (PhysEd)*
B Williams *BPsych*
M Wood *BA Maths (Hons), MA, MBCS, CITP*
Dr D Wong *PhD (Psych)*

Awards

K Allen Australian Postgraduate Research Award
K Butler NHMRC Aboriginal and Torres Strait Islander Travel Scholarship
Dr S Byrne NHMRC Research Fellowship - Australian Public Health
H D'Antoine NHMRC Aboriginal and Torres Strait Islander Health Research Scholarship
G Dixon New Investigators Award (Perinatal Society of Australia and New Zealand) 2004
Dr J Freemantle Healthway Public Health Post-doctoral Research Fellowship.
Dr E Glasson UWA Supplementary Travel Grant 2004.
Dr E Glasson 2005 Raine Research Prize.
Dr E Mattes NHMRC General Practice Fellowship (Inaugural winner)
Dr E Mattes NHMRC Capacity Building Grant (Team investigator)
Dr W Oddy NHMRC Career Development Award in Population Health 2005 - 2009
Professor S Zubrick, Professor S Silburn, Associate T Wilkes, Dr D Lawrence Award for best-practice in health promotion research - WA Health Promotion Foundation for "The Western Australian Aboriginal Child Health Survey"

External Committees

State

Professor C Bower WA Perinatal and Infant Mortality Committee Deputy Member 1988 - 1992, Member 1993-
Professor C Bower WA Confidentiality of Health Information Committee, deputy member 2003-
Professor C Bower Scientific Sub-Committee of the Human Research Ethics Committee, Curtin University of Technology 2000-
Professor C Bower Western Australian Genetics Council, Department of Health WA, 2001-
Professor C Bower Prenatal Diagnosis Committee, Department of Health WA, 2001-
Professor C Bower Western Australian Neurosciences, foundation member of Interim Board, 2004-
Dr E Blair Shaken baby syndrome steering committee, initiated by the WA Child Protection Council
Dr E Glasson Board member, WA Autism Diagnostician's Forum (2004-)
Dr J Freemantle Member Executive St George's Cathedral Foundation of the Arts.
Dr J Freemantle Examining Chaplain, Anglican Church of Australia, Western Australia
Dr J Freemantle Fellow of the Guildford Grammar School Council
Dr J Freemantle Examiner for Faculty of Medicine and Dentistry
Dr J Freemantle Member SIDS and Kids Scientific Advisory Committee
Dr J Freemantle Member of Executive, Perinatal Indigenous Network SIG
Dr J Freemantle Member, Western Australian Executive Public Health Association of Australia
Dr D Lehmann Vaccine Impact Surveillance Network Committee, WA, 1998 –
Dr D Lehmann Meningitis Centre Committee 1998-
Dr R Skinner Royal Australasian College of Physicians, Scientific Program Committee
Dr R Skinner Medical Advisory Committee, PMH
Dr R Skinner Research & Education Committee, PMH
Associate Professor E Wilkes National Advisory Group on Aboriginal and Torres Strait
Islander Health Information and Data (NAGATSIHID): Special Indigenous Advisor
Associate Professor E Wilkes NIDAC: Chairperson
Associate Professor E Wilkes International Collaborative Indigenous Health Research Project (ICIHRP): Investigator
Associate Professor E Wilkes Rio Tinto Partnership: Program Leader
The National Advisory Committee
The Operational Management Committee
The Internal Management Committee
The Project 2 and 3 Committee
Associate Professor E Wilkes Data Principles Working Group (Department of Health and Ageing): Member
Associate Professor E Wilkes Western Australian Aboriginal Child Health Survey: Chairperson
Associate Professor E Wilkes Curtin University Centre for Aboriginal Studies Advisory
Committee: Member
Associate Professor E Wilkes Derbarl Yerrigan Health Service inc.: Board member
Associate Professor E Wilkes Kulunga Research Network, Telethon Institute for Child Health: Advisor
Associate Professor E Wilkes Marr Mooditj Foundation: Executive Committee member

National

Professor C Bower Australian Birth Defects Society 1999 -
Professor C Bower Australian Paediatric Surveillance Unit Scientific Review Panel 1998-
Professor C Bower Australian Paediatric Surveillance Unit Board 1998-, Chair (2003-)
Professor C Bower National Child Health Information Advisory Committee (AIHW) 1998-
Dr S Byrne Member of The Australian Child and Adolescent Obesity Research Network (ACAORN) (2004)
Dr S Byrne Co-chair of the ACAORN Longitudinal Studies Special Interest group (2004)
Dr S Byrne Member of the Australian Eating Disorders Research Interest Group (2004)
H D'Antoine NHMRC Palliative Care Committee
Professor N de Klerk Australian Radiation Health and Safety Advisory Council, 1999-
Professor N de Klerk Executive Committee, Australian Twin Register, 2001-
Professor N de Klerk Australian NHMRC Asbestos Working Party, 2003-

Professor N de Klerk Australian Working Group developing Radiation Protection Standard for Exposure to ELF, 2003-
Dr J Freemantle Member Child and Youth Intergovernmental Partnership – National Public Health Partnership
Dr J Freemantle Member ATSI Working Group -Child and Youth Intergovernmental Partnership
Dr J Freemantle Member, Australian and New Zealand Perinatal Society
Dr J Freemantle Member, Public Health Association Australia
Dr J Freemantle Executive Aboriginal and Torres Strait Islander Special Interest Group Public Health Association Australia
Dr J Freemantle National Vice-President (policy) – Public Health Association Australia
Dr J Freemantle Member of the Australian Epidemiology Association
Dr H Leonard Australian Association of Developmental Disability Medicine (2003-)
Dr W Oddy Baby Friendly Hospital Initiative National Advisory Committee - Invited position 2003-2005.
Dr W Oddy National Food & Nutrition Monitoring Project, Breastfeeding Reference Group (Australia) Invited position - ongoing.
Professor S Silburn National Suicide Prevention Advisory Committee
B Williams National Suicide Prevention Advisory Committee
Professor S Zubrick National Mental Health Promotion and Prevention Working Party
Professor S Zubrick National Youth Statistics Advisory Committee

Regional

K Butler Office of Aboriginal Health, Aboriginal Health Promotion Strategy Working Party
H D'Antoine External Advisory Committee, Curtin University Centre for Aboriginal Studies
H D'Antoine Combined Universities Centre for Rural Health PHCRED Program Steering Committee
Professor N de Klerk Clinical Drug Trial Committee, Sir Charles Gairdner Hospital, 1986-88, 1990-
Professor N de Klerk Mesothelioma Committee of Western Australia - co-ordinating the Western Australian Mesothelioma Register, 1989-
Professor N de Klerk Busselton Population Medical Research Foundation, Board, 1997-
Professor N de Klerk Busselton Population Medical Research Foundation, Scientific Committee, 1998-
Professor N de Klerk Western Australian Air Quality Co-ordinating Committee Health Issues Group, 1998-
Professor N de Klerk Management Committee, Data Linkage Project, Health Department of WA, 2001-
Professor N de Klerk Executive Committee, Data Linkage Project, Health Department of WA, 2001-
Professor N de Klerk Medical and Scientific Advisory Panel, Cancer Foundation of Western Australia, 2001-
Professor N de Klerk Primary Health Care Research Evaluation and Development Unit Advisory Panel, UWA, 2002-
Professor N de Klerk Western Australian Medical Radiation and Cancer Working Party, 2004-
Dr H Leonard Public Health Association, WA Branch, 2001 –
K Miller Mental Health Promotion Action Link
Dr W Oddy Baby Friendly Hospital Initiative Advisory Committee (WA) - Invited position 2003-2005.
Dr W Oddy Breastfeeding Public Health Action Group, Health Department of WA 1997 to 2005.
Dr W Oddy Eat Well Move Well WA Implementation Committee, Health Department WA 2004-2006.
Professor S Silburn WA Ministerial Advisory Council on Child Protection
B Williams Youth Focus Action Research Reference Group
B Williams Scoping Project: Older people and depression (Office of Seniors Interests and Volunteering)
B Williams Linkz Suicide Prevention Program Committee Member

International

Professor C Bower International Clearinghouse for Birth Defects Surveillance and Research. 2004 -, Secretary (2004-)
Dr D Lehmann Scientific Committee for the 4th International Symposium on Pneumococci and Pneumococcal Diseases, Helsinki, May 2004.
Dr D Lehmann Scientific Committee of the XVI Lancefield International Symposium on Streptococci and Streptococcal Diseases, Cairns, September 24-27, 2005.
Dr D Lehmann Co-Director of the 5th International Symposium on Pneumococci and Pneumococcal Diseases, Alice Springs, 2006.

Invited presentations

Dr E Blair Can we reach consensus? Linda Watson, Eve Blair, Noula Gibson, Sarah Love, Peter Flett. Interobserver variation on the classification of bilateral spastic cerebral palsy. Conference workshop at annual AACPDM Meeting March 2004. Melbourne.
Dr E Blair Measuring Adiposity with special reference to children. April 15th, 2004. Grand Round, Princess Margaret Hospital.
Dr E Blair Epidemiology and aetiology of the cerebral palsies – plenary session. Australian Paediatric Neurology Conference. Margaret River, May 9th 2004
Dr E Blair Medico-legal issues in cerebral palsy. Australian Paediatric Neurology Conference. Margaret River, May 9th 2004
Dr E Blair Can we reach consensus? (Interobserver variation on the classification of bilateral spastic cerebral palsy for the Australian National CP Register). Linda Watson, Eve Blair, Noula Gibson, Sarah Love, Peter Flett.Cerebral Palsy Conference, July 2004, Washington, USA 2004.
Dr E Blair Research Methodology for therapists. Seminar in Dept of physiotherapy, Princess Margaret Hospital, July 20th 2004.
Dr E Blair The ethics of conducting research with vulnerable people. CP Week Symposium on Research Collaborations, Cerebral Palsy Association, Coolbinia, August 17th 2004.
Professor C Bower Mandatory fortification of food with folate for the prevention of neural tube defects: the value of data from a birth defects register.

Division of Population Sciences

International Symposium on Congenital Malformations. Kyoto, Japan, 2004.
Professor C Bower What do we know about alcohol in pregnancy and its effects in Australia? 32nd International Medical Advisory Group Conference. Canberra, 2004.
Professor C Bower Fetal Alcohol Syndrome. Royal Australian College of Physicians Annual Scientific Meeting, Canberra May 2004.
Professor C Bower Birth defects after ART. Serono Symposium: "Unravelling Fetal Programming and The Influence of ART", Adelaide, October 2004.
Professor C Bower Fetal Alcohol Syndrome. Intergovernmental Council on Drugs. Perth, September, 2004.
Professor C Bower Neural tube defects and the politics of prevention. Perspectives in Child Health Series. Perth, 2004.
K Butler Why Maternal and Child Health?, Aboriginal Health Conference, Perth, 30 June 2004
Dr S Byrne The Childhood Growth and Development Study. Australian Association for the Study of Obesity National Conference, Brisbane, August 2004
Professor N de Klerk Western Australian Goldminer Studies. Epidemiological Perspectives on Silica and Health, New York, 2004.
Professor N de Klerk The Silica Standard in Australia. Epidemiological Perspectives on Silica and Health, New York, 2004.
Professor N de Klerk Mesothelioma survival in Western Australia. 1st Perth Mesothelioma Centre Symposium, Perth, 2004.
Professor N de Klerk Privacy considerations and the Western Australian Twin Register. Australian Twin Register, Annual Conference, Perth, 2004.
Professor N de Klerk Health effects of ELF EMF: a review of the epidemiological evidence. ESAA EMF Scientific Workshop - EMF Science and Standard Setting, Melbourne, 2004.
Professor N de Klerk Malignant Mesothelioma in Western Australia. Thoracic Society of Australia and New Zealand (WA Branch) Annual Scientific Meeting, Mandurah, 2004
Dr J Freemantle Forensic Enquiry from an epidemiological perspective. Forensic Police Continuing Education Series, Perth. 2004
Dr J Freemantle Have we got it right? Address for Launch of Red Nose Day
Dr J Freemantle Where do WW Infants and children die, 1980-2003. GIS Health research Forum, Perth 2004
Dr J Freemantle Overview of infant and childhood mortality by WA health region's. ConferWest Lecture series.2004
Dr J Freemantle Reviewing WA mortality among infants and children. Grand Round, Princess Margaret Hospital.2004
Dr J Freemantle 18years of mortality data – How can we help? Centre for Clinical Research in Neuropsychiatry. UWA 2004
Dr J Freemantle Patterns, Profiles and Trends in Deaths occurring in infancy in WA. Institute for Child Protection.2004
Dr G Kendall, Professor S Zubrick, Associate Professor Blair E. Latency and pathway effects of family life stress on mental health in Australian Children. The 3rd Conference Of Epidemiological Longitudinal Studies in Europe, Bristol (Sept 2004).
M La Puma Binge eating in obese children. Australian Association for the Study of Obesity National Conference, Brisbane, August 2004
Dr H Leonard "Rett syndrome research in Australia-past, present and future." Child Neurology Study Group, Margaret River, May 2004.
Dr H Leonard "InterRett: international developments in Rett syndrome research." Annual Scientific Meeting of the Royal Australian College of Physicians, Canberra, May 2004.
Dr H Leonard "Future Horizons Rett Syndrome Conference." Ottawa, Canada, October 2004.
Dr H Leonard "Rett syndrome research in Australia -past, present and future" Barcelona, Spain, October 2004.
Dr H Leonard "InterRett - the application of bioinformatics to international Rett syndrome research", Annual Conference of the Royal Australiasian College of Physicians, Canberra, May 2004
Dr H Leonard "Genotype and early development in Rett syndrome: the value of international data", Genes West 28th Annual Scientic Meeting of the Human Genetics Society of Australiasia", Fremantle, August 2004
Dr H Leonard "InterRett - IRSA Rett Phenotype Database", Ontario Rett Syndrome Assocation/International Rett Syndrome Association Future Horizons Conference, Ottawa, October 2004
Dr H Leonard "Genotype and early development in Rett syndrome: the value of international data", 33rd Annual Meeting of the Child Neurology Society, Ottawa (Canada), October 2004 (Poster)
Dr J Li Impact of demographic and socioeconomic changes on rural Chinese families. Demographic Transition, Family, and Social Integration. Institute for Health Sciences, Kunming Medical College, Kunming, Yunnan, China. 18 October 2004.
Dr J Li The ARC Linkage Project. National Data Linkage Round Table. Brisbane, Queensland, 24 May 2004.
Dr J Li, W Oddy, G Kendall, S Henderson, J Downie & L Landsborough Maternal psychosocial wellbeing and breastfeeding. Australasian Epidemiological Association Conference (Oct 2004).
Dr E Mattes Future challenges for social epidemiology: what can innovation theory teach us? Research Seminars in Epidemiology, Mailman School of Public Health, Columbia University, New York, October 2004.
Dr E Mattes Do the institutional determinants of innovation have a role in social epidemiology? National Center for Children and Families Seminar Series, Columbia University, New York, November 2004.
Maxine Croft, Eve Blair, Nick de Klerk, Anne Read and Louisa Alessandri (deceased) "Stillbirth and SIDS in Western Australia (WA) during 1980 to 1992 inclusive: progress towards understanding."
H Moore. N Leonard 'Update of Rett syndrome research', ICHR Population Sciences Away Days, Perth, March 2004
H Moore "InterRett - the application of bioinformatics to international Rett syndrome research", Neuroepidemiology Seminar Series, Perth, March 2004
H Moore, C Laurvick "Optimising follow-up in the Australian Rett Syndrome Study (AussieRett) and the IRSA Rett Phenotype Database (InterRett)", Perth Epidemiology Group Annual Meeting, Rottnest Island, May 2004
H Moore InterRett - the application of

bioinformatics to international Rett syndrome research", Genetics and Population Health Annual Conference, Fremantle, August 2004
H Moore "InterRett - the application of bioinformatics to international Rett syndrome research", 33rd Annual Meeting of the Child Neurology Society, Ottawa (Canada), October 2004 (Poster)
H Moore "InterRett - IRSA Rett Phenotype Database", Rett Syndrome Association of UK Family Weekend, Northampton (UK), October 2004
Dr W Oddy Breastfeeding, immune disease and allergy 14th International Conference, International Society for Research in Human Milk and Lactation, Cambridge, UK Sept 10-14th 2004.
Dr W Oddy Omega 3 fatty acids and asthma in children, Australian Institute of Food Science and Technology, Food Allergen Seminar, Perth, WA, June 17th 2004
Dr W Oddy Baby Friendly Hospital Initiative, Lactation Training Program, St John of God Hospital, Perth Western Australia, July 2004.
Professor Stephen Zubrick, Associate Professor Kate Taylor Analysis methods for investigating the genetics of language disorders held in Phoenix, Arizona in 2004 sponsored by the US Merril Foundation.
M.L. Rice, S.R. Zubrick, & T.C. L. (2004, November). LOOKING at Language: Plans and Preliminary Progress: Paper presented at the at the Australasian Society for Psychiatric Research Conference (Neurogenetics Workshop).
Professor S Silburn, K Miller Community and professional services consultation in suicide prevention. Invited presentation to the Australia-Japan Partnership meeting. Suicide Prevention: Culture, Community and Care. Sydney 15-26 November Melbourne.
Professor S Silburn A scientific review of the New Zealand government's "Towards Wellbeing" national suicide prevention program to improve the identification, treatment and ongoing support of youth at risk of suicide who have had contact with the child protection services of the New Zealand Department of Child Youth and Family Services.
Dr D Silva Health advantages of swimming pools for Aboriginal children in 2 remote W.A. communities. The Australasian Society for Infectious Diseases annual scientific Meeting. Alice Springs, 8-12 May 2004.
Dr R Skinner Update on HPV vaccines and future vaccination programs. WA Clinical Oncology Group Symposium: Role of HPV in Genital Neoplasia, Perth March 05
Dr R Skinner Immunising adolescents against HPV: new strategies to prevent cervical cancer. Grand Rounds, Princess Margaret Hospital, December 04, Perth
Dr R Skinner "Adolescent immunisation against HPV- new vaccines and new strategies" Meet the Experts session at Royal Australasian College of Physicians Annual Scientific Meeting, Canberra May, 2004
Dr R Skinner Rising Stars Symposium, Women's and Infants Research Foundation, KEMH, September 2003
Associate Professor E Wilkes Health Inequalities, Environmental Health and Sustainable Indigenous Communities5th National Indigenous Environmental Health Conference Terrigal NSW November 2004
Associate Professor E Wilkes Indigenous Health Services – a lecture for students in the Masters of Health Economics Course at Curtin University, 29 April 2004
Associate Professor E Wilkes Telethon Institute for Child Health Research Away Days Building Partnerships 30/31 March 2004
Associate Professor E Wilkes Institutional Racism: Are our institutions racist? Panel discussion Social Justice Network UWA 27 February 2004
Associate Professor E Wilkes, Al-Yaman F Australia's Health: Vital statistics, Vital signs AIHW Conference, Canberra June 2004
Associate Professor E Wilkes, S Bell Nurturing the leaders of tomorrow: are they born or made? Presentation to the Social Determinants of Indigenous Health Forum, Darwin, March 2004
Associate Professor E Wilkes, S Bell The NAACHO development as a response to the social determinants of health, Presentation to the Social Determinants of Indigenous Health Forum, Darwin, March 2004
E Wilkes and M Scrymgour For Susan ISPCAN Conference, Brisbane 20 September 2004
Professor S Zubrick The 3rd International Scientific Meeting of the WHO/CDC for the development of international population indicators of mental health held in Brisbane in early 2003.
Professor S Zubrick National planning forum - Ottawa in 2003 to develop a research framework for the proposed Canadian Indigenous Child Health Survey.

Postgraduate students

K Allen *B.A. (Hons), PhD candidate*
K Carville *BSc(Hons), Masters in Applied Epidemiology Candidate*
J Cesario *Psychology, PhD candidate*
A. Professor D Forbes *MBBS FRACP, PhD candidate*
K Graham *Ph.D candidate*, School of Public Health, Curtin University of Technology 2002-2005. Kathleen took leave from her position in Canberra to work on the Perth Infant Feeding Study.
M Hansen *BSc, MPH, PhD candidate*
R Huang *AMBBS FRACPDCH, PhD candidate*
B Hulme *B.Sc (Hons) M.Psych Candidate*
R Jamieson *B.A. (Hons) M.Psych Candidate*
J Joseph-Bowen Paediatrics, *PhD candidate*
E Klaric *B.Psych M.Psych Candidate*
M La Puma *BA Hons, M.Psych*
C Lynch *B.Psych M.Psych Candidate*
S Mihrshahi *Ph.D candidate*, Centre for International Health, Curtin University of Technology 2004- 2006. Seema won a Curtin University APA scholarship to conduct her research into breastfeeding and mortality prevention in Madagascar (2004-2006)
N Pingault *BSc(MedSci)(Hons1), MASM, MAIMS, PhD* Nevada
WS Pomat *BSc(Hons), MSc, PhD Candidate*
S Love *Ph.D*
N Sloan *BSc Hons, PhD candidate*
F Watt *B.Psych M.Science Student*
B Williams *MSc (ClinPsych)* – thesis submitted, grade pending. Charles Sturt University 2004. Implicit Theories of Youth Suicide Held by Professionals and Para-Professionals: Does the 'Gatekeeper' Youth Suicide Prevention Training Program Change These Implicit Theories?
Z Ellis *Masters of Midwifery*

Division of Population Sciences

Theses passed

Dr H Alfonso PhD, University of WA, 2004 Progression and prognostic factors of asbestos-related diseases in a cohort exposed to asbestos in Western Australia.
K Allen B.A. (Hons) University of Western Australia 2004. Weight Status, Weight and Shape Concern, and Psychological Well-Being
A Arumugaswamy BMed Sci with distinction, Department of Medicine, University of Melbourne. Investigation of passive smoking in the causal pathways for otitis media in Aboriginal and non-Aboriginal children in the Kalgoorlie-Boulder region.
C Gray B.A. (Hons) University of Western Australia 2004. Global and Domain Specific self-esteem in healthy weight, overweight and obese children
M La Puma M.Psych (Clinical) University of Western Australia 2004. Binge eating in obese children: Prevalence, pathways and psychopathology.
K Miller MHP Curtin University of Technology 2004. Help seeking behaviours of suicidal men aged 17-35 years
Dr S Poerwanto PhD, University of WA 2004: Inequality of infant mortality in Indonesia: evidence-based information and its policy implications.

Visitors

Professor T Achenbach
E Elliott
J Francis Scientist
Dr E Haan
Dr C Hagquist Visiting fellow
Professor W Hall Visiting fellow
Professor N Henley Visiting fellow
Dr C Hertzman University of British Columbia
Dr J Kurinczuk, *BSc, MBChB, MSc, MD, FFPH, FAFPHM, DLSHTM* Consultant Clinical Epidemiologist
Dr A Leach Menzies School of Health Research
Professor Allan Cripps, Griffith University
N Leonard
Dr X Liu
M Miller
C O'Leary
Dr S Phuanukoonnon Research Fellow, Papua New Guinea Institute of Medical Research
Dr D Ravine
Professor J Reeder Papua New Guinea Institute of Medical Research
Professor L Rescorla
H Wright

Division of Virology

Overview

Research undertaken within the Division of Virology focuses on understanding how viruses cause disease within the central nervous system (CNS). This research covers a range of activity, including molecular studies of viral replication, studies of the pathogenesis of viral encephalitis using animal models, the development of community surveillance for viruses causing CNS infections and the development of improved diagnostic methods. These studies overlap extensively and involve all staff within the Division in some capacity.

Murray Valley Encephalitis

Reverse genetic studies on the molecular pathogenesis of Murray Valley encephalitis virus infection

Peter McMinn, Robert Hurrelbrink

Many mutations affecting the virulence of Murray Valley encephalitis virus (MVE) and related flaviviruses are located in the immunodominant envelope (E) protein. Superimposition of these mutations on the three-dimensional structure of the protein clearly identifies clusters of mutations with the potential to effect protein structure and function. Our laboratory has focused on two such regions - an Arg-Gly-Asp (RGD) motif, located on the lateral face of the putative receptor binding region of the protein, and a Ser-Ser-Ser (SSS) motif, which forms part of a hinge region believed to be involved in low-pH induced conformational change during virus fusion. Mutations in these regions markedly reduce the ability of MVE to cause encephalitis in the mouse model and in some cases perturb the fusion activity of the E protein.

Using reverse genetics we have engineered panels of virus mutants with specific amino acid substitutions to investigate the nature of this attenuation. Some mutations in the RGD motif cause a complete loss of neuroinvasiveness, but have no effect on virus binding and/or entry, despite the fact that similar motifs in other viruses (such as adenovirus and foot and mouth disease virus) have been implicated in the binding of virus particles to host-cell integrins. We believe that mutations in this region may instead affect the correct folding of the protein in the endoplasmic reticulum. Alternatively, the interaction of E with other virus proteins such as prM may be perturbed, preventing prM from fulfilling its role as a protective inhibitor of virus fusion during egress.

Like mutations in the RGD motif, mutations in the SSS motif also affect neuroinvasiveness, however a reduction in the haemagglutination activity these viruses further suggests that a defect in virus fusion is involved in the observed attenuation. Hydrophobic amino acid substitutions in this motif may prevent the correct reorganisation of the E protein at low-pH in the endosome. Alternatively, such mutations may disrupt the receptor-ligand interaction and prevent fusion of the viral and endosomal membranes.

We are continuing our studies on virus fusion using an infectious cDNA clone of MVE, as well as a sub-viral particle system to generate non-infectious but fusion active empty virus particles. It is hoped that such studies will shed light on the functional basis for attenuation in the encephalitogenic flaviviruses.

Enterovirus encephalitis

International collaborative study of the molecular epidemiology of enterovirus 71 in the Asia – Pacific region

Peter McMinn, Lara Herrero, Sharon Sanders, Dominic Dwyer (Westmead Hospital, Sydney), William Rawlinson (Sydney Children's Hospital), Mary Jane Cardosa (UNIMAS, Sarawak, Malaysia), Kwai Peng Chan (Singapore General Hospital), Doosung Cheon (National Institute of Health, Seoul, Korea), Eveline Irawan (Public Health Virology Laboratory, Surabaya, Indonesia), Phan Van Tu (Pasteur Institute, Ho Chi Minh City, Vietnam), Peter Siba (PNG Medical Research Institute, Papua New Guinea

Since 1997, several large epidemics of EV71 infection have occurred in the Asia-Pacific region, the first being reported in Sarawak (Malaysian Borneo) in 1997, followed by smaller outbreaks in Peninsular Malaysia and Singapore. As with previous EV71 epidemics, numerous cases of HFMD were reported, with neurological complications arising in a small proportion of cases. In addition, many cases of brainstem encephalitis associated with pulmonary oedema and a high case-fatality rate were also described during these outbreaks. Twenty-nine fatal cases of this disease were reported in Sarawak and twelve in Peninsular Malaysia. During 1998, a large EV71 epidemic occurred in Taiwan in which 405 cases of severe neurological disease and 78 fatal cases of brainstem encephalitis and neurogenic pulmonary oedema were reported. In 1999, a large EV71 epidemic occurred in Perth, Western Australia (WA) and included fourteen cases of severe neurological disease, including three with severe neurological sequelae requiring prolonged hospitalisation and rehabilitation. EV71 epidemic activity has continued in the region during 2000-2001, with EV71 isolation from cases of HFMD and encephalitis in Sarawak, Peninsular Malaysia, Singapore and WA.

EV71 isolates are passaged on rhabdomyosarcoma (RD) cells and viral RNA extracted from cell culture supernatants. The complete VP1 gene of EV71 is amplified by reverse RT-PCR assay in two overlapping amplicons using previously published primers and assay conditions. VP1 is one of the most variable regions within the enterovirus genome and has proved to be the most valuable region for determining phylogenetic relationships, both within and between enterovirus serotypes. VP1 gene cDNA is sequenced on both strands by cycle sequencing reactions using the ABI Prism Dye Terminator Cycle Sequencing Kit. The VP1 gene nucleotide and deduced amino acid sequences are aligned and phylogenetic trees constructed by the neighbour-joining method. Previously sequenced EV71 strains (deposited in the GenBank database) are also included in the analysis.

This study is providing valuable information on the origin of recent epidemic strains of EV71 and may also identify neurovirulent virus lineages for further genetic and phenotypic analysis. A five-year Wellcome Trust/NHMRC International Collaborative Research Grant supports this study. We are also using this grant to train scientists from developing countries in the Asia-Pacific region in molecular methods of EV71 surveillance. For example, we recently trained several scientists from the Pasteur Institute, Ho Chi Minh City (HCMC), Vietnam, in an intensive workshop conducted within the laboratory of Dr Jane Cardosa, UNIMAS, Sarawak Malaysia in October 2004. Following this, the HCMC group has commenced a study of the molecular epidemiology of EV71 in southern Vietnam in collaboration with us and with funding support from our Wellcome Trust. NHMRC ICRG grant.

Studies on the molecular genetics of enterovirus 71 encephalitis

Peter McMinn, Chee Choy Kok, Lara Herrero, Beng Hooi Chua, Robert Hurrelbrink, Sharon Sanders, Darren Shafren (University of Newcastle)

Recent increases in the frequency and magnitude of enterovirus 71 (EV71) epidemics in Southeast Asia have provided the impetus for studies of the molecular genetics of EV71 virulence and pathogenesis with a view to developing a vaccine. This is an area in which my research group has considerable expertise. The first step in EV71 vaccine development has been the construction of an infectious cDNA clone. The complete sequence of two local EV71 strains has been determined and full-length infectious cDNA clones have been constructed.

We have also developed a collaboration with Associate Professor Darren Shafren, Picornavirus Research Unit, The University of Newcastle, with the aim of identifying the cellular receptor for EV71. Identification of the EV71 receptor will allow us to develop a small animal model of EV71 encephalitis by construction of a transgenic mouse incorporating the EV71 receptor gene into the mouse genome. This model will allow a detailed study of the pathogenesis of EV71 encephalitis, as we have done for MVEV. It will also enable us to test the immunogenicity and efficacy of candidate live attenuated vaccine strains derived from mutagenesis of the EV71 infectious cDNA clone. A NHMRC Project Grant and a Wellcome Trust grant support this study.

Staff and Students

Head of Division

Peter McMinn *BMedSc (Hon) MB, BS PhD FRCPA FRCPath DipRACOG*
Clinical Associate Professor
Discipline of Microbiology
School of Biomedical and Chemical Sciences
The University of Western Australia
Clinical Virologist and NHMRC Practitioner Fellow,
Princess Margaret Hospital for Children

Research Staff

Chee Choy Kok *BSc (Hon) PhD*
NHMRC Senior Research Fellow
Robert Hurrelbrink *BA BSc (Hon) PhD*
Wellcome Trust Senior Research Fellow
Sharon Sanders *BSc (Hon)*
NHMRC Graduate Research Assistant

Students

Beng Hooi Chua *BS PhD candidate (UWA)*
Lara Herrero *BSc (Hon) PhD candidate (UWA*
Kristy Philippe *BSc (Hon) PhD candidate (UWA)*
Patchara Phuektes *MVSc PhD candidate (Murdoch)*

Visitors

Jane Cardosa, Director, Institute for Health and Community Medicine, UNIMAS, Sarawak, Malaysia

Theses passed

Kristy Philippe BSc with First Class Honours (UWA)

External committees

P McMinn Member of the W.A. State Arbovirus Control Committee
P McMinn Member of the Health Department of WA Influenza Pandemic Planning Committee
P McMinn Chair, Princess Margaret Hospital Infection Control Committee
P McMinn Member, Winter Strategies Committee, Health Department of WA
P McMinn Member, NHMRC Grant Review Panel 2B

Invited presentations

Peter McMinn. Fremantle Hospital "Hot Topics in Infection Control" Seminar, 19th March. Title: "Avian Influenza: could it be the source of the next pandemic?"
Peter McMinn. King Edward Memorial Hospital Postgraduate course in Women's Health, 4th May. Title: "Common infections in pregnancy."

Invited postgraduate examiner

Peter McMinn. Ph.D. thesis for the School of Veterinary Science, The University of Melbourne. Title: "Equine rhinitis B virus characterisation, seroprevalence, detection and isolation in Australia. Author: Mr Wesley David Black.
Peter McMinn. B.Med.Sc thesis for the Faculty of Medicine, Monash University. Title: "Revisiting Murray Valley Encephalitis: Histological and Molecular Studies of Archival Tissue." Author: Mr Yang David Tran

Research Collaborations

Developmental Immunobiology Group

Overview

The research programme in Developmental Immunobiology focuses on the processes which influence the developing human immune system, particularly processes which predispose to allergic diseases and asthma in early childhood. With strong clinical and laboratory activities our group is ideally placed to investigate to underlying immunological mechanisms, and to also examine clinically relevant applications and practical solutions. This includes a number of clinical intervention studies for the *prevention* of allergic diseases. In broad terms the projects focus on:

- Fetal immune responses which predispose to immune dysfunction (particularly allergy)
- Maternal influences on immune development (*in utero*)
- Early life environmental factors which may predispose or help prevent the development of asthma and allergic diseases

Since this independent group was established in 1999 we have had enormous success with NHMRC funding (with successful grants every year). We have established and consolidated strong local and international research collaborations (in Europe and North America). We have also consolidated several major links with industry (particularly our relationship with VRI Biomedical which has been very of significant mutual benefit).

This year our studies on the effects of diet modification on immune development have received international attention and we have received further NHMRC funding to pursue these next year. Susan Prescott also received a NHMRC Career development Award (2004-2008) which has allowed her which allowed her to release her administrative commitments as Head of School of Paediatrics and Child Health (UWA) to focus more on research. She also received a JJ Billings Fellowship from the Royal Australiasian College of Physicians and has had 6 invitations to international conferences as a Keynote or Plenary speaker. She had 19 press interviews with the news media in 2004 on topics related to our research. Dr Dunstan returned to Australia in 2004 after postdoctoral in the UK (with Prof John Warner's group in Southampton). She now has an academic appointment with the UWA School of Paediatrics and Child Health, and has already been successful with a number of research grants (including NHMRC, Asthma Foundation, and Ada Bartholomew Grants). She was also awarded a 3 year fellowship from the Child Health Foundation. As our many cohort studies grow, we will soon have over 1000 children enrolled in our various studies. Jasmine Roper (research assistant) continues to play an important role in coordinating the follow up studies. Liza Breckler and Heidi Lehman joined our group as research assistants in 2004 and Liza will be undertaking a PhD in 2005. Angie Taylor and Paul Noakes also continue to make major contributions to the group activites and are expected to submit their PhD theses in the next 12 months.

Environmental modification for the treatment or prevention of allergic disease

The role of probiotic bacteria in the prevention of allergic disease

Angie Taylor (PhD student), A/Prof Susan Prescott, Dr Jan Dunstan

Collaborators: Prof Patrick Holt, A/Prof Patricia Conway
Funding: NHMRC, VRI Biomedical

With escalating morbidity and mortality from asthma and associated allergic diseases, there is a pressing need to identify contributing environmental factors with the capacity to promote allergic immune responses. The potential importance of changing early microbial exposure has been specifically highlighted by international authorities, both as a potential contributing factor to recent increases in allergic disease, and as a strategy for primary disease prevention. This study will address the influence of gastrointestinal flora on infant immune development and how modifications in flora may alter the expression of the expression of the T helper cell type 2 (Th2) allergic phenotype in high risk infants. With growing public interest, and one controversial report suggesting a clinical benefit (1), there is an urgent call to investigate the role of probiotic bacteria in allergy prevention, particularly to assess immunological effects. There is also a pressing need to investigate the enormous potential for events at mucosal surfaces to influence immune development. We aim to demonstrate that the proposed n--on-specific immunomodulatory effects of probiotic bacteria have broad ranging effects on many aspects of early immune development. We will provide a detailed analysis of effects on mucosal immune development and systemic immune responses to mucosally encountered antigens (including bacteria and allergens).

Using a randomised double blind placebo controlled trial design, this study will assess the effects of probiotic supplementation for the first 6 months of life, in babies at high risk of atopy. We have already recruited our target population of almost 200 infants who have received either a probiotic (Lactobacillus acidophilus) supplement (n=90) or placebo (n=90). We are now in the process of following these infants to assess the effects on a) infant faecal colonisation patterns, b) developing mucosal immunity, c) specific systemic immune function, and d) clinical outcomes (allergy, infection, respiratory colonisation, and serous otitis media). Preliminary results are expected by the end of 2005.

The effects of n-3 fish oil supplementation (n-3 PUFA) in pregnancy on infant immune development allergic disease.

Dr Jan Dunstan, A/Prof Susan Prescott

Collaborators: Prof Laurie Beilin, Dr Trevor Mori, Dr Anne Barden, Dr Peter Hartman, Dr Leon Mitoulas, Prof Karen

Simmer.
Funding: NHMRC

This NHMRC funded study has received international attention and so far there are 13 publications arising from this work (below). The main objective was determine if maternal dietary supplementation with n-3 PUFA during pregnancy can modify immune responses in infants, in the context of developing future allergy prevention strategies. In a randomised controlled trial 98 atopic pregnant women received fish oil (3.7g n-3 PUFA/day) or placebo from 20 weeks gestation until delivery. Neonatal PUFA levels and immunological response to allergens were measured at birth. (See figure 1). 83 women completed the study. Fish oil supplementation (n=40) achieved significantly higher proportions of n-3 PUFA in neonatal erythrocyte membranes (mean 17.75 $\pm$ SD 1.85 % total fatty acids) compared to the control group (n=43) (13.69 $\pm$ 1.22 %, P < 0.001). All neonatal cytokine (IL-5, IL-13, IL-10 and IFN__ responses (to all allergens) tended to be lower in the fish oil group (statistically significant only for IL-10 in response to cat). Although this study was not designed to examine clinical effects, we noted that infants in the fish oil group were three times less likely to have a positive skin prick test to egg at 1 year of age (OR 0.34, 95% CI 0.11, 1.02, P=0.055). Although there was no difference in the frequency of atopic dermatitis at 1 year of age, infants in the fish oil group also had significantly less severe disease (OR 0.09, 95% CI 0.01, 0.94, P=0.045). These data suggest potential reduction in subsequent infant allergy following maternal PUFA supplementation.

More detailed follow up studies are required in larger cohorts to establish the robustness of these clinical findings, and to ascertain their significance in relation to longer term modification of allergic disease in children. We have just received NHMRC funding for 2005-2008 to assess this in a larger cohort (below).

Publications so far:

1. Dunstan J, Prescott SL. Does fish oil supplementation in pregnancy reduce the risk of allergic disease in infants. Current Opin in Allergy and Immunol (*accepted Jan 2005*).
2. Prescott SL, Dunstan J. The role of omega 3 fatty acids in immune development and allergy prevention. Eds Frank Colombus, Nova Science, New York (*accepted Feb 2005*)
3. Prescott SL, Dunstan J, Immune dysregulation in allergic respiratory disease: The role of T regulatory cells. Pulm Pharm Therapeutics. (*Accepted Dec 2004*)
4. Prescott SL, Dunstan J, The role of prenatal events in the development of allergic disease, In: Fetal Origins of disease, Nova Press, *(Accepted Oct 2004)*
5. Hatfield HM, Dunstan JA, Holt PG, Hayes L, Sehmi R, Denburg J, Prescott SL. Fish oil supplementation in pregnancy modifies neonatal progenitor numbers and responsiveness to IL-5 in infants at risk of atopy. Pediatric Research 2005; 57(2):276-281.
6. Dunstan JA, Mori TA, Barden A, Beilin LJ, Holt PG, Philip Calder, Taylor AL, Prescott SL. The effects of omega-3 polyunsaturated fatty acid supplementation in pregnancy on fetal and maternal erythrocyte fatty acid composition. Eur J Clin Nutr, 2004; 58(3) 429-437.
7. Prescott SL, P. Calder. Omega 3 fatty acids and allergic disease. Curr Opin Clin Nutr Metab Care 2004 ; 7 : 123-9.
8. Barden A, Mori TA, Dunstan JA, Taylor AL, Thornton CA, Croft KD, Beilin LJ, Prescott SL. Fish oil supplementation in pregnancy lowers F2 Isoprostanes in neonatal at high risk of atopy. Free Radical Research, 2004: 38(3): 233-239.
9. Dunstan JA, Roper J, Mitoulas L, Hartmann PE, Simmer K, Prescott SL. The effect of supplementation with fish oil during pregnancy on breast milk IgA, sCD14, cytokine levels and fatty acid composition. Clin Exp Allergy 2004; 34:1237–1242.
10. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy. J Allergy Clin Immunol 2003;112:1178-84.
11. Dunstan JA, Mori TA, Barden A, Beilin

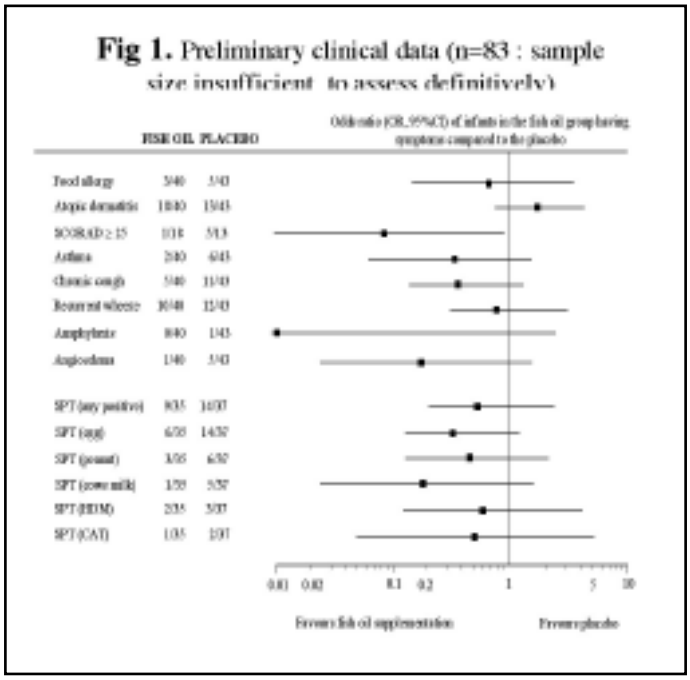

Figure 1

Research collaborations

LJ, Taylor AL, Holt PG, Prescott SL. Maternal fish oil supplementation in pregnancy reduces IL-13 levels in cord blood of infants at high risk of atopy. Clin Exp Allergy. 2003; 33: 422-448.

12. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. The Effect of Maternal Fish Oil Supplementation on Neonatal Immune Responses. Clinical Immunology and Allergy in Medicine. 2003. 409-412.
13. Prescott SL, Taylor AL, King B, Dunstan J, Upham JW Thornton CA, Holt PG. Neonatal IL-12 capacity is associated with variations in allergen specific immune responses in the neonatal and postnatal periods. Clin Exp Allergy 2003;33:566-572.

The use of n-3 fish oil supplementation in infancy for the prevention of allergic disease.

Dr Jan Dunstan, A/Prof Susan Prescott

Collaborators: Dr Trevor Mori, Dr Anne Barden, Prof Tony Ferrante, Dr Charles Hii.
Funding: NHMRC

As indicated above, we have just received NHMRC funding for 2005-2008 to assess the potential role of fish oil in the prevention of allergic disease in infancy, based on out previous studies (above). In this proposed study, we will start n-3 PUFA supplementation at birth (n=165) and assess the effect on earlier indicators of allergy including sensitisation to foods and atopic dermatitis, compared to placebo (n=165). This will also determine if very early postnatal supplementation is as effective as supplementation in pregnancy. The study will commence early in 2005.

The role of probiotic bacteria in the treatment of atopic dermatitis

Stephanie Weston (Telethon Fellow), Dr Jan Dunstan, A/Prof Susan Prescott

Collaborators: Dr Peter Richmond, Dr Anne Halbert
Funding: Telethon (Fellowship), VRI biomedical

This study assessed the effects of probiotics infants (n=53) aged 6-18 months with moderate or severe atopic dermatitis. They were randomised to receive either probiotic ($3x10^9$ L fermentum PCC™, [VRI Biomedical]), or equivalent volume of placebo, twice daily for eight weeks. A follow-up assessment at sixteen weeks was performed.

There was no significant difference between the probiotic and placebo group in any of the baseline characteristics (age, gender, initial SCORAD, steroid usage, daycare attendance, use of yoghurts). Significantly more children receiving probiotics (n=24, 92%) showed an improvement from their baseline SCORAD index at week 16 compared with the placebo group (n=17, 63%) (p=0.01). At the completion of the study the probiotic group had a significantly lower mean SCORAD index (24.8, SE 2.5) compared to placebo (35.3, SE 3.2) (p=0.01). The same significant changes were seen for the modified SCORAD [31] which does not include the parent's subjective score (shown in figure 2). The mean percentage improvement in SCORAD index at the end of the study period (week 16) was twice as great in the probiotic group (37%) as in the placebo group (17.6%) although this was not statistically significant (p=0.08). There was no significant difference between the groups in the mean amount of topical corticosteroid applied at each time point, nor in the mean change over the course of the study (p=0.27). Of note, children on probiotics had less lower respiratory tract infections (p=0.04). Although the significance of this is not clear, it is possible that this could indicate other effects on immune competence. This is also the first study to show persisting benefits 2 months after the supplementation was ceased. Possible mechanisms of this sustained effect may relate to persistent changes in faecal flora and / or persistent immunological effects. This will be addressed in ongoing immunological analysis of this population and further long term studies (which are the subject of current NHMRC applications).

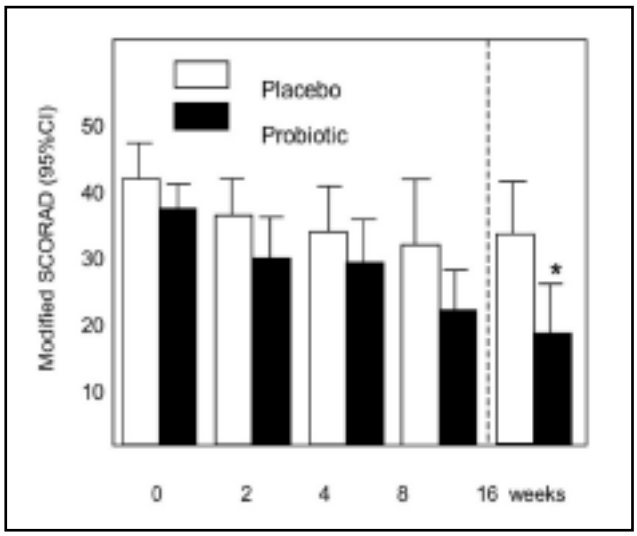

Figure 2

Publications so far:

1. Weston S, Halbert A, Richmond P, Prescott SL. Probiotics in atopic dermatitis: a randomised controlled trial. *Arch Child Disease (accepted November 2004)*.

The effects of maternal smoking on fetal and postnatal immune development

Paul Noakes (PhD student), Dr Jan Dunstan, A/Prof Susan Prescott

Collaborators: Prof Bob Mead, Dr Sunalene Devadason

This study addresses the effects of maternal cigarette smoking in pregnancy

on the developing immune system and the subsequent risk of allergic disease. To date, most studies have concentrated on the effects of smoking on lung mechanics rather than local and systemic effects on immune function and inflammation. Preliminary data from our group (see listed publication) suggest that in addition to altered airways development, exposure to cigarette smoke *in utero* may also adversely affect immune development. This was the basis for this larger cohort study to address this in more detail. We now have cryopreserved samples (including cord blood mononuclear cells, serum, urine and saliva) from a new cohort (n=120) of women who smoked (n=60) and who did not smoke (n=60) in pregnancy and we are now performing the laboratory analyses on these. The results of this study are expected in the next 6 months.

Publicatiions so far:

1. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. *Allergy* 2003, 58:1053-1058.

The effects of antioxidant supplementation on immune responses of allergic adults

Dr Jan Dunstan, Jasmine Roper, Heidi Lehmann, A/Prof Susan Prescott

Collaborators: Prof Tom Riley, Prof Prue Hart
Funding: Asthma Foundation

Although there have been long-standing claims about the health benefits of naturally occurring antioxidant Vitamins, there is still very limited information on the proposed immune effects, despite the fact that these products are used widely in the community to enhance immune function in a range of conditions. This novel study will explore these claims by examining the effects of these products on a range of immune parameters, both *in vivo* and *in vitro*. we completed recruitment of adult volunteers in late 2004 (n=45). The effect of dietary (*in vivo*) supplementation will be determined by comparing immune responses to allergens, microbial antigens and mitogens "before" and "after" the intervention. In other studies the *in vitro* effects of various antioxidants will also be assessed by adding these agents to the cell cultures. The results of these studies are expected in mid 2005.

Materal fetal interactions in pregnancy as determinants of immune development.

The role of the placenta in early immune development

Liza Breckler (PhD student), Dr Jan Dunstan, Dr Adrian Charles, A/Prof Susan Prescott

Collaborators: Prof Patrick Holt
Funding: Ada Bartholomew grant (UWA), Princess Margaret Hospital Seeding Grant

This novel study will explore the basic mechanism by which variations in placental immune function can influence fetal immune development and the risk of subsequent allergic disease, which now affects 40% of the population. As the immunologically active interface between the fetus and the mother, the placenta is a major source of cytokines and other immune mediators detected in the fetus. Our preliminary studies have shown associations between the levels of placenta derived cytokines and the risk of subsequent allergic disease, and we also have preliminary evidence that materno-fetal interactions influence both fetal immune development and the risk of allergic disease (see Background). We speculate that variation in both the propensity for inflammatory responses, and / or the capacity to regulate these is of key importance in establishing early patterns of fetal immune responsiveness and disease risk. While cord blood studies provide indirect evidence that levels of immune mediators formed by the placenta correlate with subsequent allergic disease there are virtually no studies *directly* examining placental function in this context. We propose that events that alter placental immune function also directly influence fetal immune function, subsequent immune development and disease susceptibility. This study will provide extremely valuable novel mechanistic data on the relationship between perintal events and immune development.

The role of the materno-fetal interactions in early immune development

Liza Breckler (PhD student), Dr Jan Dunstan, Jasmine Roper, Amira Wahden A/Prof Susan Prescott

Collaborators: Dr Cathy Thornton (Jones), Prof Patrick Holt
Funding: NHMRC

This novel NHMRC funded study is examining the role of maternal/fetal immune interactions as a plausible controlling mechanism for Th1 immune maturation in early life. We are specifically assessing the relationship between the pattern of maternal responses to fetal HLA antigens and the the developing pattern of fetal responses. The effects of parity (previous exposure to "foreign" paternal antigens) and maternal atopy (propensity for Th2 responses) are also being assessed in this context. To do this we are comparing the responses of atopic and nonatopic mothers, and multigravid and primigravid women. Responses in pregnant (2^{nd} and 3^{rd} trimester) and non pregnant states will be compared in these groups to look for differences in "immune adaptation" in pregnancy. These early interactions provide an essential basis for determining pathways of influence by environmental agents, many of which may exert effects in pregnancy. Recruitment and sample collection has now been completed, and the results of this study are expected in 2005.

Publications so far (further publications anticipated):

1. Prescott SL, Irwin S, Taylor A, Upham JW, Burgner D, Richmond P. CpG fail to Th1-polarise neonatal mononuclear cell responses to allergens. Clin Exp Allergy (accepted Jan 2005).

Research Collaborations

Staff and Students

Head of Group

Susan L Prescott *PhD MBBS B Med Sci FRACP*
Associate Professor, Department of Paediatrics, The University of Western Australia
Honorary fellow, Telethon Institute for Child Health Research
Paediatric immunologist, Princess Margaret Hospital for Children

Research Staff

Jan Dunstan *PGDip BAppSc. PhD*
Jasmine Roper *BSc (Hons)*
Heidi Lehmann *BSc (Hons)*
Liza Breckler *BSc (Hons)*

Postgraduate Students

Angie Taylor *BSc (Hons) PhD Candidate*
Paul Noakes *BSc (Hons) PhD Candidate*
Angie Taylor *BSc (Hons) PhD Candidate*
Khema Liyange *BSc (Hons) PhD Candidate*
Stephanie Weston *MBBS, Masters of Public Health Candidate*

Research Support

Renee Dallimore

Theses passed

Jan Dunstan PhD University of Western Australia 2004. Studies of maternal diet in pregnancy to prevent allergy: The effects of maternal n-3 PUFA (fish oil) supplementation on infant immune responses

Awards

S Prescott. NHMRC Career Development Award, 2004 – 2008
S Prescott. JJ Billings Fellowship
S Weston. Best Scientic Presentation, Australasian Society of Clinical Immunology and Allergy, Queensland 2004.
J. Dunstan. Child Health Foundation fellowship

External Committees

International

Susan Prescott. EAACI Section on Pediatrics: Allergy Prevention Working Party

National

Susan Prescott. National Asthma Council: Asthma Management Handbook Working party
Susan Prescott. Paediatric Interest Group: Australasian Society of Clinical Immunology and Allergy
Susan Prescott. Allergy Prevention Working Party: Australasian Society of Clinical Immunology and Allergy

Invited Presentations

Susan Prescott. Invited speaker: (Plenary) Beijing International Symposium on Allergy: The Upper and Lower Airway link, Beijing Tongren Hospital, China October 2004
Susan Prescott. Invited speaker (Plenary / Keynote): Allergy Society of South Africa, Cape Town, South Africa (one of 2 international guests to the meeting), August 2004
Susan Prescott. Invited speaker (KeyNote): Malaysian Congress of Allergy and Clinical Immunology, Kular Lumpar, Malaysia, April 2004
Susan Prescott. Invited speaker (Postgraduate course): Basic and Clinical Allergy, Imperial College London, UK, April 2004
Susan Prescott. Invited speaker (Plenary): Symposium on Specific Allergy, London UK, April 2004
Susan Prescott. Invited speaker : National Vaccine meeting (Festschrift), Sydney, Feb 2004

Diabetes Research

Overview

Type 1 diabetes in childhood is a common chronic metabolic disease of unknown cause that can affect children of all ages. The incidence of Type 1 diabetes continues to increase. Type 2 diabetes is also on the increase as a consequence of the increasing prevalence of obesity in childhood. The diabetes research program addresses questions relevant to both these forms of diabetes.

The mainstay of management of Type 1 diabetes is insulin treatment, which attempts to restore blood glucose levels to as close to normal as possible. This is the most effective way to prevent the devastating long-term complications of the disease. Unfortunately this is difficult to achieve and insulin therapy is frequently associated with low blood glucose or hypoglycaemia. Hypoglycaemia results in unpleasant symptoms if mild and if severe, can produce convulsions or unconsciousness. Fear of hypoglycaemia is ever present for the patient and their family. It not only impairs quality of life but importantly restricts attempts to control diabetes.

A major goal of our research is to address the problem of hypoglycaemia and examine ways to treat diabetes more effectively. The program of research brings together an active team of experienced investigators from different fields to address this important clinical problem. By improving diabetes control anticipate that in turn this will contribute to diabetes complication prevention as well as reducing the burden of this disease on the patient and on his or her family.

A second thrust of research in the diabetes division is to study the epidemiology of diabetes. In WA, every child with diabetes is managed at our centre. The causes of diabetes are as yet unknown and the reason for its increase is unknown. There are genetic influences on the aetiology of type1 diabetes as well as an unknown environmental trigger. This research aims to study the pattern of type 1 diabetes development and factors that may be associated with it.

A third focus is childhood obesity and Type 2 diabetes. We are collaborating with other investigators at the Institute for Child Health Research to examine the causes of obesity in childhood. In addition the section is involved in several lines of research studying the pathophysiological derangements that develop in obese children. This research is headed by Dr Elizabeth Davis who is also collaborating with the department of human movement UWA to study the impact of exercise on the metabolic disturbances that develop in this group of children.

Staff and Students

Head of Group

Timothy W Jones *MD MBBS DCH FRACP*
Associate Professor, Telethon Institute for Child Health Research
Head of Department, Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children

Principal Investigators

Elizabeth A Davis *MBBS FRACP*
Chief Investigator, Senior Lecturer, Telethon Institute for Child Health Research
Consultant, Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children

Dr. Paul Fournier *PhD*
Chief Investigator, Department of Human Movement and Exercise Science, UWA

Associate Professor Steve Stick *PhD, MB BCIR, MRCP (UK), FRACP*
Chief Investigator, Department of Respiratory Medicine, Princess Margaret Hospital for Children

Research Staff

Aris Siafarikas *PhD*
Patricia Gallego *MD*
Aveni Haynes *MBBChir*
Sarah Mc Mahon *MBBS, FRACP,*
Luis Ferreira *PhD*
Max Bulsara *BSc (Hons), MSc*
Joanna Elliot Bpsych, *MPsych (App. Dev), MPsych (Clinical)*

Postgraduate Students

Kym Guelfi *BSc (Hons)*
Ray Davey *BSc (Hons)*
Vanessa Bussau *BSc (Hons)*

Research Support

Nirubasini Ratnam *BSc (Hons)*
Leanne Youngs *BSc*
Alisha Thompson *BSc*
Vanessa Baker *BSc*
Alison Climie *BSc (Hons)*
Bronwen Clements
Dee Marangou *RN*
Jill Loveday *RN*

Awards

M Bulsara, Travel Grant. Juvenile Diabetes Research Foundation, 2003
A Haynes, Travel Grant. Juvenile Diabetes Research Foundation, 2004
A Haynes, Travel Grant. European Association for the Study of Diabetes, 2004
EA Davis, Diabetes Australia Research Trust Grant, 2005
L Ferreira, Travel Grant. Juvenile Diabetes Research Foundation, 2004
L Ferreira, Fellowship. Juvenile Diabetes Research Foundation, 2004
EA Davis, TW Jones, National Heart Foundation Grant-in-Aid
TW Jones, EA Davis, S Stick
NHMRC/JDRF Program Grant 2003-2007
EA Davis, S Byrne, TW Jones, S Zubrik
Healthway. 2005-2007

External Committees

International

TW Jones Member Scientific Review Committee, JDRF International 2001-2004

National

TW Jones JDRF Australia, Scientific Advisory Committee 1999-2004
TW Jones Australian National Association of Diabetes Centres- paediatric representative 1999-
TW Jones Australian Growth Hormone Advisory Committee 2000-, Chairperson 2003-

Research Collaborations

TW Jones Member Australasian Paediatric Endocrinology Group Council 2001-
TW Jones Member Scientific Review Committee Diabetes Australia Research Trust 2004-
EA Davis Member Examinations Committee. RACP

Regional

TW Jones Member Medical Advisory Panel, Diabetes Research Foundation of Western Australia 2002-
EA Davis, Boardmember, Diabetes Research Foundation of Western Australia 2004-

Invited Presentations

Bussau, V.A., A. Baptista, L.D. Ferreira, L.M. Youngs, T.W. Jones and P.A. Fournier. A short maximal sprint effort prevents an insulin-mediated fall in glycaemia in type 1 diabetes. Exercise, Muscle and Metabolism Conference. Deakin University, Melbourne, Australia, 12-14 November, 2003, p. 27.

Bussau, V.A., L.D. Ferreira, T. Jones and P.A. Fournier. The effect of a 10-second sprint on exercise-mediated fall in glycaemia in individuals with type 1 diabetes mellitus. Proc. Fourteenth Annual Combined Biological Sciences Meeting, Rendezvous Observation City Hotel, Scarborough, Western Australia, 22 August, 2003, p. 60.

Ferreira, L.D.M.CB., V.A. Bussau, T. Jones and P.A. Fournier. Can a short maximal sprint effort be used as a tool in the acute management of blood glucose levels in type 1 diabetes? Proc. Fourteenth Annual Combined Biological Sciences Meeting, Rendezvous Observation City Hotel, Scarborough, Western Australia, 22 August, 2003, p. 19.

Fournier, P.A., V. Bussau, A. Baptista, L. Ferreira, L. Youngs, T. Jones and E. Davis. A short maximal sprint effort acutely prevents glycemia from falling in type 1 diabetes. Diabetes, Vol. 52, Suppl. 1, 63rd American Diabetes Association Scientific sessions, New Orleans, Louisiana, 13-17 June, 2003, p. A235.

Guelfi, K., T. Jones and P.A. Fournier. Effect of intermittent exercise on glycaemia in individuals with type 1 diabetes during peak insulin action. Exercise, Muscle and Metabolism Conference. Deakin University, Melbourne, Australia, 12-14 November, 2003, p. 36.

Guelfi, K.J., T. Jones and P.A. Fournier. Management of glycaemia during intermittent exercise and recovery in individuals with type 1 diabetes. Proc. Fourteenth Annual Combined Biological Sciences Meeting, Rendezvous Observation City Hotel, Scarborough, Western Australia, 22 August, 2003, p. OP 3B.

Davis EA, Trundle CL, Ives J, Robins PD, Jones TW. High Prevalence of Structural CNS Abnormalities in Children with Early onset Diabetes. Presented at the American Diabetes Association Annual 62nd Annual Meeting, San Francisco. June 2002

Bulsara MK, Holman DJ, Davis EA and Jones TW, Modelling hypoglycaemic count data with extra observed zeros, presented at the International Diabetes Federation Meeting, Paris, 2003.

Strudwick SK, Gardiner JR, Foster JK, Carne CL, Davis EA, & Jones TW. The long term impact of severe hypoglycaemia on cognitive function in early onset Insulin Dependent Diabetes Mellitus, Presented at the International Diabetes Federation Meeting, Paris, 2003.

Johnston RJ, Caplin N, O'Leary PJ, Jones TW, Davis EA. Early and permanent loss of the glucagon response to hypoglycaemia in adolescents with type 1 diabetes, presented at the International Diabetes Federation Meeting, Paris, 2003.

Gallego PH, Carne C, Davis EA, Jones TW. Hypoglycaemia in diabetic children and adolescents with impaired and normal awareness. Presented at the International Diabetes Federation Meeting, Paris, 2003.

Jones TW Australian Diabetes Educators Association Annual Scientific Meeting, September 2003. Invited speaker. Meet the Expert : CGMS it has a place in diabetes management.

Jones TW Australasian Paediatric Endocrine Group, Melbourne, September 2003. Invited Speaker: Hypoglycaemia in children - ?an uncommon problem.

Davis EA Australasian Paediatric Endocrine Group, Melbourne, September 2003. Invited Speaker: Insulin pump therapy.

Jones TW Australian Association of Clinical Biochemists Annual Scientific Conference. September 2003. Invited Speaker: In vivo continuous glucose monitoring.

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