



*imagine....*

PREVENTION  
INNOVATION  
DEDICATION



# Telethon Institute for Child Health Research

## Who we are

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

We are housed in a purpose-built research facility on the outskirts of the Perth CBD and have close to 400 staff and students.

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

## What we do

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

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

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

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

## Our mission

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

## Our aims

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

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# *imagine....*

*if every child was given the chance to be all that they can be.*

The fact is that many children begin life with the odds already against them. Some face chronic, debilitating or life-threatening diseases.

Others are born with disabilities that present a life-long challenge to them, and to their families.

An increasing number battle profound economic and social disadvantage as the disparity between the haves, and the haves-not, increases.

Why is it, at a time of increasing technology and affluence, many of the key indicators reflecting the health and well-being of children are either static or getting worse?

Why is it that mental health problems such as ADHD, eating disorders, youth suicide and risk-taking behaviours are increasing?

Why are we seeing such high rates of pre-term births, diabetes, asthma, autism and cerebral palsy?

We don't, for a minute, **imagine** that the answers to these questions will be simple.

But we do know that we won't find the answers unless we apply our scientific rigour in new ways.

That's why our Institute brings together hundreds of researchers from a diverse range of different scientific disciplines to tackle the big issues in child health in bold and imaginative new ways.

**From the realms of imagination into reality**  
– the Telethon Institute for Child Health Research.

**PREVENTION INNOVATION DEDICATION**



# Division of Cancer Biology

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. Additionally, 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 library (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 expression 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 two types of genetically manipulated mouse models, which have SCL function removed in early brain development. It is hoped that these brain SCL knockout mice 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

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D Izon, M Smeets, J Göthert

It is already known that 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 Ick promoter to specifically overexpress SCL in developing T cells. Using this model system we hope to be able to uncover the underlying causes of SCL-driven T cell leukaemia. Preliminary results suggest that a specific subpopulation of cells may be protected from cell death even before leukaemia is detectable.

Using the SCL stem enhancer to mark haemopoietic stem cells and their progeny

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D Izon, J Göthert

Evidence for the lineage relationship between embryonic and adult hematopoietic stem cells (HSCs) in the mouse is primarily indirect. In order to study this relationship in a direct manner, we expressed the tamoxifen-inducible Cre-ERT recombinase under the control of the stem cell leukemia (Scl) stem-cell enhancer in transgenic mice (HSC-SCL-Cre-ERT). To determine functionality, HSCSCL-Cre-ERT transgenics were bred with Cre reporter mice. Flow cytometric and transplantation studies revealed tamoxifen-dependent recombination occurring in more than 90% of adult long-term HSCs, whereas the targeted proportion within mature progenitor populations was significantly lower. Moreover, the transgene was able to irreversibly tag embryonic HSCs on days 10 and 11 of gestation. These cells contributed to bone marrow hematopoiesis 5 months later. In order to investigate whether the de novo HSC generation is completed during embryogenesis, HSC-SCL-Cre-ERT-marked fetal liver cells were transplanted into adult recipients. Strikingly, the proportion of marked cells within the transplanted and the *in vivo*-remaining HSC compartment was not different, implying that no further HSC

generation occurred during late fetal and neonatal stages of development. These data demonstrate for the first time the direct lineage relationship between midgestation embryonic and adult HSCs in the mouse. Additionally, the HSC-SCL-Cre-ERT mice will provide a valuable tool to achieve temporally controlled genetic manipulation of HSCs.

#### Use of retroviral cDNA library screening to discover new genes causing T cell leukaemia

D Izon, M Smeets, A Chan

This project entails introduction of a library of genes from normal immature T cells into mice which have a block in T cell maturation (T cell roadblock). These mice have a block in normal T cell maturation that is easily identifiable by flow cytometry.

Already some of the T cell leukemia causing genes are known to bypass this T cell roadblock and allow normal T cell maturation. This bypass is also easily identified by flow cytometry. Therefore, by introducing libraries of genes into the T cell roadblock mouse model we will be able to discover new T cell leukemia genes by detecting a bypass around this roadblock. Once identified, new T cell leukemia genes from this application will allow the development of more specific T cell leukaemia drugs. Eventually, this targeted approach will hopefully increase the survival rate and also decrease the need for aggressive chemotherapy in all T cell leukaemias.

#### 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 the CNS implies an important yet undefined function for Scl in brain cells.

Detailed investigation into the cellular phenotype of mature Scl-expressing neurons in midbrain and hindbrain elucidated the type of neurons

that expresses Scl. This is thought to contribute to a better understanding of Scl function during embryogenesis and after birth. We have identified a change in cellular phenotype from developing to mature neurons, which supports the view that the role of Scl in neurons after birth is essentially different from its earlier role during brain development.

Our loss of function approach through conditional deletion of Scl during embryogenesis in neuronal-Scl deleted mice is an alternative way to unravel Scl function in CNS. We have shown that embryonic deletion of Scl results in a striking phenotype after birth. The survival rate of these mice after birth was severely affected: they were significantly growth retarded and displayed a hyperactive behaviour from pwn2 onwards. Moreover, lacZ staining had disappeared almost completely from hindbrain and was significantly reduced in caudal thalamus and midbrain. These observations were quantitatively verified at weaning age. However, less intense LacZ staining in the mid-hindbrain was already apparent at E12.5, indicating that some Scl null neurons are lost already early in brain development. Our study to address potential functional compensation by Tal2, a homologous bHLH factor to Scl, is still underway. The functional implications of loss of Scl neurons were studied with a focus on control of respiration, anxiety and daily activity patterns. The overall research results in this study ascribe a crucial role to Scl as a neurogenic factor in neuronal differentiation of a specific population of mid-hindbrain neurons.

# Division of Cancer Biology

## Staff and Students

### ■ Head of Division.

David Izon BSc (Hons) PhD

Adjunct Senior Lecturer, University of Western Australia.

### ■ Research Staff

J. Anke M van Eekelen. Adjunct Senior Lecturer, University of Western Australia.

Monique F.M.A. Smeets. PhD. Research Fellow

### ■ Postgraduate Students

Angela Chan BSc (Hons). PhD Candidate

Elena Takano. BSc. MSc Candidate

Tina Röhn (visiting student to complete MSc Candidature at Lund University, Sweden)

Tegan Ollivierre BSc. Hon Candidate

### ■ Research Support

Kelly Becher. BSc(Hons). Research Assistant

Lan Doan. BSc. Research Assistant

Samantha Dagger. BSc(Hons). Research Assistant

## Theses passed

Cara Bradley PhD with Distinction, University of Western Australia 2004. Cell fate determinant characteristics of the transcription factor SCL in blood and brain.

## External Committees

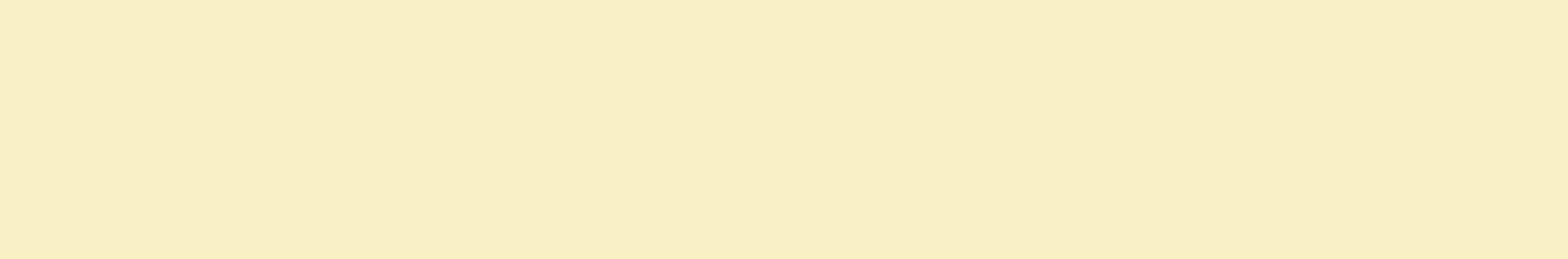
### ■ National

David Izon. NHMRC Development Grant Committee. 2004.

J.A.M. van Eekelen. Australian and New Zealand Society for Cell and Developmental Biology. WA representative.

## Invited Presentations

J.A.M. van Eekelen. Embryonic expression of SCL is required for normal brain development. 25th Australian Neuroscience Society annual meeting, Perth, Febr 2005



# Division of Cell Biology

The principal focus of research in the Division of Cell Biology is on elucidation of the cellular and molecular mechanisms underlying resistance and susceptibility to inflammatory diseases in the respiratory tract, in particular those caused by allergy and infections. Earlier work from the Division has established an important development paradigm in paediatric medicine, notably that risk for postnatal development of atopy and asthma 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 maturation of a variety of cytokine driven effector functions which are suppressed in utero in order to protect the placenta from inflammatory damage. These same mechanisms are necessary for resistance to both infections and allergy, and we have shown that the rate at which they mature functionally during the preschool years is a key determinant of risk for allergy, respiratory infection and asthma. Much of the work of the Division is targeted at more detailed definition of these mechanisms, with the aim of development of early intervention strategies 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 to understand the mechanisms which normally control cell populations in the airway wall that are responsible for triggering the “late phase response” in asthma. This part of the asthmatic 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.

## Aetiology and pathogenesis of atopy and asthma

### Immunoprophylaxis of asthma and atopy

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

Over the last three years we have been 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. The trial will test a radical approach to prophylaxis of these diseases in “high risk” children, employing a vaccine-like approach which is conceptually similar to that used for prevention of infectious disease. This process has involved exhaustive protocol development negotiations with NIH and the US Food and Drug Administration, with final approval being granted in March 2006. 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 in the areas of the trial centres in Australia, USA, Sweden and Germany (notably house dust 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.

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

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

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

We are approaching completion of the respiratory component of the 13 year follow-up of the W.A. Pregnancy Cohort, which was initially recruited in 1989 to investigate the effects of fetal monitoring on pregnancy outcome. In this phase of the study, we are targeting 1,500 cohort members, with the aim of discriminating asthma and allergy phenotypes. The study is examining the clinical history, genetic profile, lung physiology and immunology of the participants. Immunological assays being performed include allergen skin prick testing, eosinophil counts, and measurement of IgE and IgG4 to seven different allergens, eosinophil cationic protein and soluble CD14 from plasma, and leukotriene metabolites in urine. In addition, we are investigating both allergen-specific T-cell immunity and global measures of immune competence. The last study subjects will be processed during April 2006, and we envisage completion of the bulk of the *in vitro* analyses by mid year. After completion of the main part of the lab component, the focus of the work will shift to statistical analysis and modelling of the data obtained. The long term aim is to integrate the information collected to identify biomarkers which discriminate asthma subgroups, and to subsequently develop algorithms utilising these biomarkers which will serve as aids in diagnosis, prognosis and treatment choice for asthma and allergy.

This research is funded by the Stanley Trust UK.

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

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J Rowe, D Suriyaarachchi, M Serralha, C Ladyman, A Sadowska, and PG Holt in collaboration with M Kusel and PD Sly, Clinical Sciences, TICHR

Earlier studies from a variety of groups including our own have presented evidence of the presence of allergen-responsive CD4+ Th-cells in cord blood. This has led to a broadly accepted hypothesis that Th-cell-sensitisation is frequently initiated in utero by transplacental transport of allergen, either as partially processed fragments or bound to maternal IgG. In collaboration with Clinical Sciences, we have tested this hypothesis in a prospective cohort study on 200 infants at high genetic risk of atopic disease, tracking their responses to house dust mite (HDM) allergen in PBMC collected at birth, and subsequently at 6, 12 and 24mths. We have observed that HDM-induced responses at birth represent non-specific responses, with true Th2-type memory responses (those specific to a positive atopic outcome at 2 years) not being seen until between 6 and 12 months. Furthermore, we have shown that these allergen-specific Th2 memory responses correspond to increased titres of IgG4 and IgE in those who are classified as atopic at age 2 years. These findings have significant clinical implications in that they represent one of the first detailed studies examining the kinetics of allergen-specific Th-cell memory response development in relation to subsequent atopy outcomes.

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

#### Identification of novel Th2-associated genes in allergen-stimulated T cells

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

We have completed the initial phase of a large scale study to identify novel genes distinguishing T-cell memory responses in atopics and nonatopics, utilising Affymetrix microarray technology, the results of which will appear in the Journal of Immunology in early 2006. This has involved kinetic studies of PBMC responses to house dust mite (HDM) allergen, and the use of cell

separation techniques to partition the responses into components attributable to CD4+ and CD8+ T cells, and cells of the innate immune system. 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 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. In particular, an "early" cluster peaking 6 to 24 hrs following HDM stimulation was identified, and was enriched for a range of genes involved in cell signalling which have not previously been recognised as part of the Th2 response profile. A second cluster peaking late (48 hrs) was enriched for genes associated with effector function. The preferential expression of these novel genes in atopics following HDM stimulation has been confirmed by quantitative RT-PCR in several independent patient populations. Analysis of the response to HDM in nonatopics suggests a "modified" Th1 expression profile, in which potentially highly pathogenic (pro inflammatory) genes, notably IFN $\gamma$  and CCL18, are differentially attenuated relative to other Th1-associated genes. Additionally, expression of the novel Th2 genes in atopic responses appears to be restricted to responses elicited at low TcR signal strength i.e. low level stimulation with native allergen as opposed to strong mitogens such as PHA or PMA/Ionomycin, which may account for failure to detect these genes in earlier published microarray studies.

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

## Innate Immunity

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

MK Tulic, and PG Holt in collaboration with Rj Hurrelbrink, Virology, TICHR

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections and is responsible for the majority of hospitalisations of children during their first 2-3

years of life. Severity of infection varies enormously in different individuals, though why this occurs is not fully understood. TLR4 is the receptor involved in bacterial (LPS)-induced signal transduction and recently it has been shown to recognise the F-protein of RSV. TLR4 is extremely polymorphic and we hypothesize that polymorphism(s) in TLR4 are associated with modified epithelial responses to RSV and LPS. Human bronchial epithelial cells were transfected with TLR4 wild type (WT) or TLR4 mutated constructs (Asp299Gly or Thr399Ile) and 48 h later stimulated with RSV or LPS. Asp299Gly or Thr399Ile transfected cells attenuated RSV and LPS-induced IL-6, IL-8, TNF- $\alpha$  and IFN $\gamma$ -induced myxovirus protein A (MxA) inflammatory responses (n=6, P<0.05). Similar inhibition was seen using UV-inactivated RSV suggesting viral replication was not required for this effect. Although intracellular TLR4 was detected by 24 h post transfection with TLR4 WT construct and was present on the cell surface by 48 h, in contrast, both Asp299Gly and Thr399Ile transfected cells failed to express TLR4 at their cell surface despite expressing normal intracellular TLR4 levels. Poor surface expression was also confirmed by the inability of these cells to bind LPS as well as reduced activation of their NF- $\kappa$ B signaling pathway when compared to WT controls. These findings were replicated in non-transfected peripheral blood mononuclear cells (PBMC) from children with TLR4 Asp299Gly or Thr399Ile polymorphisms, suggesting these polymorphisms downregulate RSV and LPS- inflammatory responses in both mesenchymal and bone-marrow derived cells. We propose that poor expression of TLR4 on PBMC from children heterozygous for the Asp299Gly or Thr399Ile results in decreased LPS binding which causes reduced NF- $\kappa$ B signaling and cytokine production. Depression of the innate immune response via this mechanism may have implications for the susceptibility of individuals to viral and/or bacterial insults. 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.

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

#### Maturation of the innate immune system

S Yerkovich, ME Wikström, D Suriyaarachchi, JW Upham and PG Holt

Early childhood is a period where there is greater susceptibility to infection due to the immaturity of both the innate and adaptive arms of the immune system. The innate immune system provides the first line of defence against invading pathogens via activation of the Toll-like receptors (TLR), which in turn generates important host defences, such as Th1 cytokine production. At birth and during early childhood, the immune response is skewed towards the Th2 phenotype, with a reduced capacity to generate the Th1 type responses seen in adults. The aim of this study was to investigate the postnatal development cytokine production capacity of the innate immune system by assessing the response to lipopolysaccharide in relation to secretion of the Th1 cytokines IL-12, IL-18, IL-23, IFN $\gamma$  and MxA (reflects type 1 interferon) and the inflammatory cytokines IL-6, IL-10 and TNF $\alpha$ . For these studies we used mononuclear cells obtained from adults, children aged 2 months and 1, 4 and 13 years of age, and from cord blood. Remarkably, for all of the Th1 cytokines studied there was a similar developmental pattern, showing reduced responsiveness to stimulation at birth and in the younger children, with adult levels not evident until 13 years of age. The inflammatory cytokines showed a similar post-natal developmental pattern from 1 yo onwards, with low levels observed at 1 yo which progressively increased with age, before reaching adult equivalence at 13 years of age. Surprisingly though, cord blood cells produced significantly higher levels of these inflammatory cytokines when compared with adults. This high production was transient, as it was no longer observed at the age of 2 months, and was not influenced by the method of delivery. Analysis of TLR4, the receptor for LPS, showed higher levels on cord blood monocytes and together with the higher number of monocytes evident in cord blood, may

account for the inflated cytokine levels produced by cord blood cells. These results indicate that the innate immune system develops slowly throughout childhood, and that adult levels are not reached until the early teenage years. One surprising outcome of this study was the high inflammatory response seen transiently in the cord blood, and the significance of this finding will be explored in detail in follow up studies.

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

#### Antigen presenting cells during infancy

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

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, 12 months and 2 years 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 RSV infections and wheezy lower respiratory tract infections during the first year of life and allergic sensitisation by age 2. 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 development of persistent asthma.

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

#### Development of T-cell memory during infancy

A Rate, PG Holt and JW Upham

DC are a key regulator of immune memory. Our studies have shown that recall memory T cell responses to both allergens and vaccine antigens in young children are constrained by DC immaturity. In 12-month-old children, T-cell memory to the vaccine antigens tetanus toxoid and diphtheria is often difficult to detect. However, we have found that addition of autologous, cytokine derived DC markedly enhances the magnitude of these

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responses, unmasking covert memory that would not be recognised using standard cell cultures. These findings have important implications for development of effective vaccines.

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

## Airway epithelial cells and regulation of dendritic cell function

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A Rate, PG Holt and JW Upham

In 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 DC activation without affecting antigen uptake by DC. Identifying the nature of these factor(s), and whether these regulatory processes are less efficient in children with asthma is the focus of ongoing studies.

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

## Inhibition of the allergic response by bacterial lipoproteins and lipopeptides

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R Taylor and John Upham in collaboration with P Richmond, School of Paediatrics and Child Health, 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 involved in recognising components of Gram-positive bacteria, and how this might regulate allergic inflammation. We have recently shown that lipoproteins and lipopeptides derived from Gram-positive bacteria markedly inhibit allergen-specific Th2 responses in atopic individuals, but have no effect on responses in non-atopic individuals, and do not inhibit responses to other antigens such as tetanus toxoid. This effect

is mediated by antigen presenting cells, but does not involve changes in IL-10 or IL-12 synthesis. Further work is needed to determine the specific mechanisms involved, but this work is likely to provide a foundation for developing new methods to treat allergic diseases such as asthma.

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

## Vaccine Studies

### Neonatal immunization with pneumococcal conjugate vaccine in Papua New Guinea

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A van den Biggelaar, M Nadal and PG Holt in collaboration with D Lehmann (Population Sciences, TICHR) and P Richmond, School of Paediatrics and Child Health, The University of Western Australia

Similar to other high-risk populations, infants in Papua New Guinea (PNG) have neonatal onset of dense respiratory tract pneumococcal (Pnc) colonisation, which is associated with increased risk of invasive pneumococcal disease and possible long-term effects on the development of protective immunity. In order to obtain the earliest possible protection against invasive diseases and reduce burden of early carriage, neonatal immunization with pneumococcal conjugate vaccine (PCV) has to be considered. With the current study in the PNG highlands we aim to provide proof of principle of the safety and immunological feasibility of neonatal PCV immunization. 312 infants are enrolled at birth and randomised to receive PCV either at 1) birth-1mo-2mo, or 2) 1mo-2mo-3mo or 3) receive only routine immunizations (control group); all children receive the 23-valent pneumococcal polysaccharide vaccine at 9 months of age. Blood samples to study cellular and humoral immunity will be taken at birth, 2-3-4 months of age, 9 and 10 months (to assess immune memory) and at 18 months at study completion. Carriage will be assessed weekly for the first month of life and at regular interval thereafter. There will be ongoing surveillance for respiratory and other diseases throughout the study. Aims include studying the effect of early carriage on the development of systemic and mucosal immunity to Pnc infections and the impact of early PCV on carriage; further our understanding of the basic

immunological mechanisms underlying conjugate vaccine responses during the critical neonatal period; and provide insights into the interactions between the developing T-cell system and vaccines against a background of intense microbial stimulation.

Recruitment of newborns in Papua New Guinea is ongoing. Currently 90 infants have been enrolled. Since no vaccine-related serious adverse events were recorded in the first 50 children that were randomised either to the PCV group of 1mo-2mo-3mo or the control group, neonatal immunisation has since been part of the randomisation schedule. Cord blood mononuclear cells and peripheral blood mononuclear cells are collected and cryopreserved in Papua New Guinea and transported to Perth, where laboratory studies to finalise test systems including T-cell methodology are in progress.

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

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

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J Rowe, S Yerkovich and PG Holt in collaboration with PD Sly, Clinical Sciences, TICHR, P Richmond, School of Paediatrics and Child Health, The University of Western Australia and RK Loh, Princess Margaret Hospital

Acellular vaccines against diphtheria tetanus and pertussis (DTaP) have been introduced in recent years, with the aim of reducing the occurrence of febrile reactions associated with the whole cell version of the vaccine (DTwP), and large clinical trials have demonstrated significantly improved safety profiles. However, it is becoming clear that children vaccinated exclusively in infancy with DTaP are more likely to experience large local reactions at the vaccination site following pre-school administration of the DTaP booster. However, the immunological mechanisms underlying this phenomenon are poorly understood and were the focus of this study. Polyclonal and vaccine-specific cellular and humoral responses were examined in a

cohort of children vaccinated exclusively in infancy with DTaP (n=30) or DTwP (n=16), and these correlated with the incidence of local reactions occurring 48 - 72 hours later. Within the DTaP vaccinated group, 43% experienced a large local reaction at the pre-school DTaP booster site in contrast to only 6% of those in the DTwP-primed group. Vaccine-specific Th2 memory responses (IL-5, IL-6 and IL-13) were associated with these large local reactions, as was a boosting of tetanus-specific IgE. Furthermore, these responses occurred more often in children who were intrinsically high Th2 responders as detected by *in vitro* responses to polyclonal stimuli prior to booster vaccination. This study suggests that priming in infancy with the DTaP vaccine promotes Th2 polarised memory responses to vaccine antigen, which in a small subset of children is associated with enhanced local reactions to booster vaccination. Follow-up studies are planned to examine the persistence of vaccine-induced Th2 polarisation.

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

## Animal model studies

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

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

Earlier published studies from this group have demonstrated that a single aerosol challenge of pre-sensitised PVG rats results in allergic airways inflammation. We have shown that cognate interactions which occur between local Th memory cells and airway mucosal dendritic cells (AMDC) trigger the rapid maturation of AMDC, assessed as an up-regulation of co-stimulatory molecule CD86 expression, which results in the accompanying expression of the full range of APC functions *in situ*. These interactions culminate in the development of airways hyper responsiveness (AHR). This sequence of events mimics the late phase response in human asthma. We have previously demonstrated that in the face of ongoing aeroallergen challenge the

# Division of Cell Biology

AMDC population returns to its constitutively quiescent state, and importantly there is no ensuing redevelopment of AHR, despite the continued presence of CD4+ Th memory cells within the airway mucosa.

An *in vitro* model of this process has been developed in PVG rats 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. Intracellular staining for FoxP3 has demonstrated a marked increase in the number of these Tr in the airway mucosa during the continuous challenge protocol. Furthermore, we have been able to isolate these cells via cell sorting and demonstrate their potent suppressive nature in an *in vitro* proliferation assay. The maintenance of protective Tr activity is dependent upon continuing allergen stimulation, as cessation of allergen exposure leads to waning of Tr number and function, release of AMDC from control and resurgence of AHR upon a single re-exposure. A further cycle of repeated daily allergen exposures results in an upgraded Tr response. Quantitative RT-PCR analysis was also used to further characterise the Tr population isolated from airway mucosa. A variety of Tr associated markers including IL-10, which have been shown in other models to be of importance in Tr activity, displayed up regulated expression. These studies have focused primarily on the PVG rat strain, which is representative of the human "non-atopic" low IgE responder phenotype. Our most recent studies have targeted the BN rat strain, a high IgE responder representative of the human "atopic" phenotype, utilising the same model of allergic airways inflammation. Preliminary data has revealed significant differences in the response of pre-sensitised animals from these 2 strains to single or multiple aeroallergen challenges. As expected the BN rats develop significantly higher IgE responses and enhanced airways eosinophilia. Similar up regulation of co-stimulatory molecule CD86 has been demonstrated on AMDC following a single challenge. However, in the face of ongoing challenge, AMDC from BN do not appear to return to their initially quiescent state as is seen in their PVG counterparts. Additionally, we have been unable to demonstrate any significant increase in the

population of Tr within the airway mucosa of the BN rats. We are continuing to study the mechanisms controlling immunological homeostasis in the airways of both PVG and BN.

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

## Dendritic Cell and T Cell Dynamics During Allergic Airways Inflammation

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

Utilising a BALB/c mouse model of experimental allergic asthma, in which increased tissue and central airway resistance is observed after aerosol allergen challenge, our recent studies have focussed on the response of airway mucosal DC (AMDC) as a major subset of cells responsible for initiating allergen-specific T cell immunity to inhaled allergens. Early activation of AMDC, within 2 to 12 hours of allergen exposure, is a characteristic feature during initiation of an asthmatic response, which returns to normal by 24 hours post-allergen exposure. This is closely accompanied by a rapid, and also transient, activation of CD4+ T cells within airway mucosal tissues. In contrast, activation of peripheral lung tissue DC is later and more sustained than their mucosal counterparts, and this is associated with the persistence of populations of activated CD4+ T cells at this site. These changes parallel the onset of the clinical symptoms of airways hyperresponsiveness. These data suggest a dynamic process of initiation of allergic airways disease, whereby transient DC and T cell activation at mucosal surfaces of proximal conducting airways leads to sustained activation of these cells in distal lung tissue sites. Future studies will focus on the regulation of DC and T cell activity within these different compartments of the respiratory tract and the roles of other cell types in contributing to antigen persistence.

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

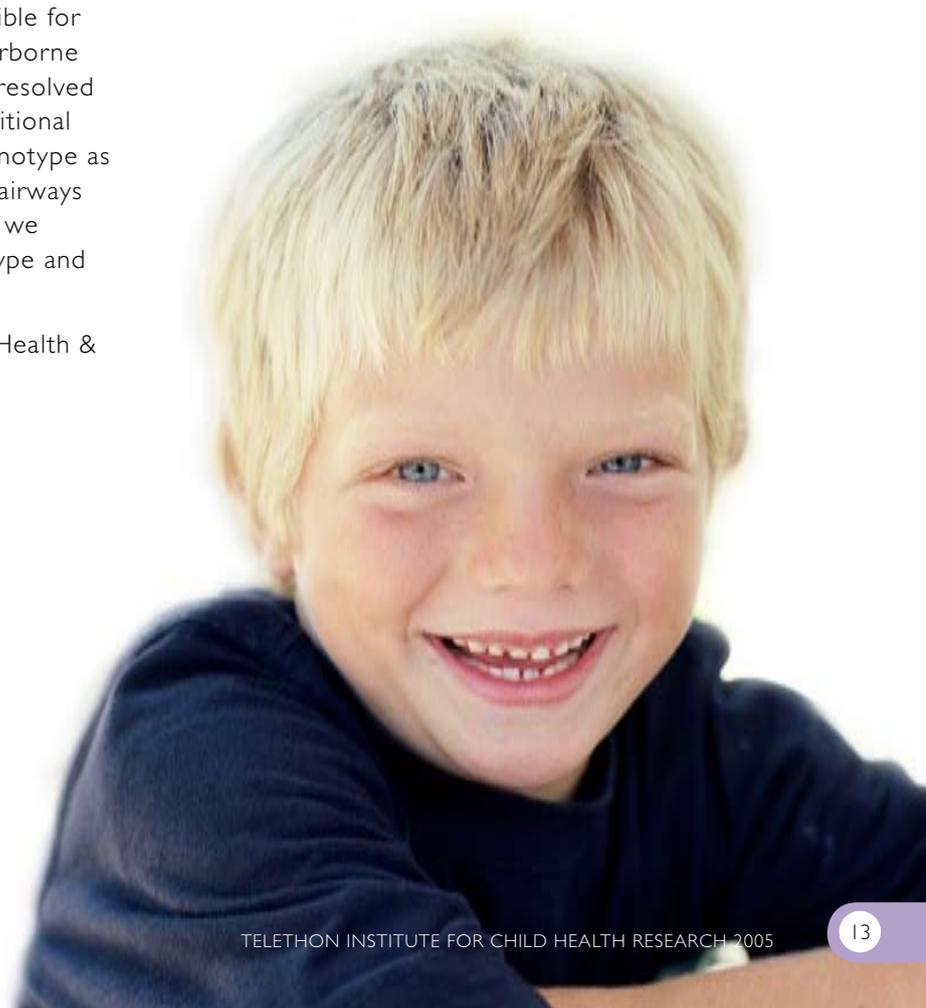
## Dendritic cells present airborne allergen in the draining lymph nodes

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ME Wikström, PG Holt, PA Stumbles

Dendritic cells (DC) form an extensive network in the airways and are able to rapidly migrate to the draining lymph nodes (DLN) where they are likely to initiate the immune response against the antigens they have captured from the airways. In order to learn more about how DC regulate the immune response against airborne allergens, we have been tracking allergen delivery to the DLN of mice using a tagged allergen preparation. Twenty-four hours after administration, most of the allergen recovered in the DLN was found in DC expressing low amounts of CD8 (CD8 $\alpha^{\text{lo}}$  DC), though small amounts were detected in a variety of other cell types, such as DC expressing high amounts of CD8 (CD8 $\alpha^{\text{hi}}$  DC), B cells, and plasmacytoid DC. Despite the range of cell types that could acquire the allergen, there was very little evidence of antigen processing by any population except CD8 $\alpha^{\text{lo}}$  DC. Moreover, CD8 $\alpha^{\text{lo}}$  DC, but not CD8 $\alpha^{\text{hi}}$  DC, were able to stimulate allergen-specific T cells *in vitro* when purified from the DLN. Thus, it appears CD8 $\alpha^{\text{lo}}$  DC are responsible for initiating the immune response against airborne allergens. Interestingly, these DC can be resolved into two populations on the basis of additional surface markers and share the same phenotype as two major DC populations found in the airways and lungs. Over the next twelve months, we will continue to characterise the phenotype and function of CD8 $\alpha^{\text{lo}}$  DC.

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



# Division of Cell Biology

## Staff and Students

### ■ Head of Division

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Patrick Holt. Scientific Advisory Board, Jenner Institute for Vaccine Research, U.K.

### ■ National

Patrick Holt. Sectional Committee for Biochemistry, Molecular Biology & Immunology, Australian Academy of Sciences.

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

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

John Upham. Asthma & Allergy Special Interest Group, Thoracic Society of Australia & New Zealand.

## Invited Presentations

Patrick Holt. The role of Dendritic Cells in virus infections. Transatlantic Airway Conference on Airway Responses to Respiratory Viruses, Key Biscayne, 2005.

Patrick Holt. Aetiology and pathogenesis of atopic asthma (Keynote Address). EAACI/SAF Annual Meeting, Davos, 2005.

Patrick Holt. Primary and secondary prevention of asthma. International Meeting on Asthma, COPD and Rhinitis Guidelines, Ferrara, 2005.

Patrick Holt. Halting the atopic march. American Academy of Allergy, Asthma and Immunology Congress, San Antonio, 2005.

Patrick Holt. Developmental factors as determinants of responsiveness to exogenous antigens in early childhood. Frontiers in Neonatal and Infant Immunity Symposium, Madrid, 2005.

Patrick Holt. Programming of sensitisation versus tolerance to allergens in early life. XVth International Meeting on Asthma, Allergy & Immunology, Instituto Argentino de Alergia e Immunologia, Buenos Aires, 2005.

Patrick Holt. Primary prevention of asthma and allergy: development of prophylactic strategies for use in high-risk children. XVth International Meeting on Asthma, Allergy & Immunology, Instituto Argentino de Alergia e Immunologia, Buenos Aires, 2005.

Patrick Holt. Maturation of immune responses in the airways of infants. American Thoracic Society Annual Meeting, San Diego, 2005.

Patrick Holt. Immune development and the pathogenesis of asthma. American Thoracic Society Annual Meeting, San Diego, 2005.

Patrick Holt. Mucosal Tolerance in infants. XIV Congress of European Academy of Allergy and Clinical Immunology, Munich, 2005.

Patrick Holt. Development of diagnostic and prognostic algorithms integrating immune response phenotypes and clinical phenotypes. XIV Congress of European Academy of Allergy and Clinical Immunology, Munich, 2005.

John Upham. Dendritic cells at the centre of innate and adaptive immunity. Keystone Symposium, Vancouver, February 2005.

John Upham. Innate and adaptive immunity to inhaled antigens. International Society for Aerosols in Medicine, Perth, March 2005.

Paediatric cancers are of a much wider spectrum compared with 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. The main aims are the identification of genetic alterations that lead to childhood cancers and the application of this knowledge to the prognosis and improved therapeutic approaches for patients. In order to examine the genetic lesions present in the various types of cancer, we make use of the microarray technology to determine gene expression profiles. The initial studies involved our panel of established leukaemia cell lines since they are ideal tools for subsequent testing of potential new drugs for the treatment of patients. Currently, a large study on primary patient specimens is in progress with the ultimate aim to achieve improved risk stratification for acute lymphoblastic leukaemia (ALL) patients and to understand the genetic basis for chemoresistance.

## Leukaemia

Prediction of relapse in paediatric acute lymphoblastic leukaemia (ALL) using 3-gene defined diagnostic classifiers

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

Despite the high cure rates, resistant forms of childhood ALL constitute a leading cause of cancer-related morbidity and mortality in children. The clinical outcome measured as 5 year event-free survival (EFS) has reached up to 85% for patients classified as standard risk (SR) and 64-75% for high risk (HR) patients. However, a substantial number of patients currently classified and treated as SR patients continue to relapse, highlighting an urgent need for a more comprehensive risk stratification at the time of diagnosis. We examined the use of gene expression profiles (GEPs) to predict long-term clinical outcome in children with ALL. We initially analysed GEPs from 55 pre-B ALL patients using HG-U133A arrays. Subsequently, a multigene classifier for outcome prediction was developed and confirmed by quantitative RT-PCR (qRT-PCR). In an independent cohort of 46 pre-B ALL patients this multigene classifier was tested using qRT-PCR. In the test cohort (n=55) supervised outcome-prediction analysis identified 18 genes that predicted outcome with a high accuracy (89%). This 18-gene classifier (18-GC) was not only significantly linked to clinical outcome, but was also more predictive of outcome than conventional parameters currently used for risk stratification. After feature selection and validation of expression levels by qRT-PCR, a defined diagnostic 3-gene classifier (3-GC) was developed based exclusively on data from the test cohort. This 3-GC was able to predict outcome in an independent validation cohort (n=46). We subsequently applied the same methodology to a cohort of T-cell ALL (T-ALL) patients and were able to identify a 3-GC to predict relapse in these patients. These studies demonstrate the feasibility of building a prognosis predictor based on GEP, to improve risk stratification in childhood ALL. This is particularly important for the identification

of patients currently stratified as SR for whom more intensive up-front treatments are already available. Currently a larger study is in progress to extend these findings. It focuses on a cohort of 50 T-ALL patients who were all treated on the same COG therapy protocol. The GEPs for these specimens were generated using the most recent and comprehensive HG-U133 Plus 2.0 microarrays (54,657 probe sets).

#### The Gene-Expression Signature of Relapse in Paediatric Acute Lymphoblastic Leukaemia: Implications for Mechanisms of Therapy Failure.

AH Beesley, AJ Cummings, JR Freitas, J Ford, 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 significant improvements in the treatment of childhood acute lymphoblastic leukaemia (ALL), the prognosis for relapsing patients remains poor. We have generated a transcriptional profile of relapsed ALL to increase our understanding of the mechanisms involved in therapy failure. RNA was extracted from 11 pairs of cryopreserved pre-B ALL bone marrow specimens taken from the same patients at diagnosis and relapse, and analysed using HG-U133A microarrays. Relapse specimens over-expressed genes involved with cell growth and proliferation, in keeping with their aggressive phenotype. When tested in 72 independent specimens of pre-B ALL and T-ALL, the identified genes could successfully differentiate between diagnosis and relapse in either lineage, indicating the existence of relapse mechanisms common to both. These genes have functions relevant for oncogenesis, drug resistance and metastasis, but are not related to classical multi-drug resistance pathways. Increased expression of the top-ranked gene (BSG) at diagnosis was significantly associated with adverse outcome. Several chromosomal loci, including 19p13, were identified as potential hotspots for aberrant gene expression in relapsed ALL. Our results provide evidence for a link between drug resistance and the microenvironment that has previously only been considered in the context of solid tumour biology.

#### The Relevance of Cell Lines as a Model for Drug-Resistance in Acute Lymphoblastic Leukaemia.

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

Cell lines are an important model system with which to examine mechanisms of drug resistance in acute lymphoblastic leukaemia (ALL), but the extent to which these lines reflect resistance phenotypes *in vivo* is not known. We have studied the sensitivity of a panel of 22 ALL cell lines to the ten drugs most commonly used in the treatment of this disease, and compared the data with that published for primary patient specimens. For most drugs, especially dexamethasone, the spectrum of *in vitro* resistance overlapped with that measured *ex vivo*. However, all cell lines were significantly more sensitive to vincristine than primary specimens, indicating that caution may be required when comparing the action of this drug *in vitro* and *in vivo*. Cross-resistance was observed between dexamethasone and all drugs except the thiopurines and methotrexate. Sensitivity to methotrexate was inversely correlated to that of the glucocorticoids and L-asparaginase, indicating a possible reciprocity in resistance mechanisms. Doubling-times for cell lines established in our laboratory (53-442 hours) were consistent with the slower growth rates that have been estimated for leukemic cells *in vivo*. A pre-B ALL cell line identified with extremely high resistance to methotrexate (IC50 >8000-fold higher than any other line) was derived from a patient receiving escalating doses of the drug, indicating *in vivo* selection of resistance as a cause of relapse. The data indicate that many of the cell lines within our panel are suitable as models with which to study naturally occurring resistance phenotypes in paediatric ALL.

## *In Vitro* Cytotoxicity of Nelarabine, Clofarabine and Flavopiridol in Paediatric Acute Lymphoblastic Leukaemia.

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

In the last 10 years only one new drug (clofarabine/ CLOF) has been approved for use in paediatric acute lymphoblastic leukaemia (ALL); two others (nelarabine/NEL and flavopiridol/FP) are currently being tested in clinical trials. We have compared in 22 ALL cell lines the *in vitro* efficacies of CLOF, NEL and FP to compounds already established in the treatment of this disease. The median IC50 (drug concentration that is lethal for 50% of cells) for CLOF across all cell lines was 7-fold lower than FP and 170-fold lower than NEL. B-lineage, but not T-lineage cell lines, were 6-fold more sensitive to CLOF than cytosine arabinoside (ARAC). The median IC50 for NEL was 30-fold and 140-fold greater than ARAC in T-lineage and B-lineage cells respectively. T-ALL cell lines were 8-fold more sensitive to NEL than B-lineage cells, but there was considerable overlap between the lineages. FP was more potent *in vitro* than DEX but at doses that Phase I/II trial experience predict will not translate into clinical efficacy. The cytotoxic response to FP was extremely similar in all cell lines. Cross-resistance was observed between the three new drugs and glucocorticoids, doxorubicin and ARAC, but methotrexate sensitivity was inversely related to that of NEL and FP. In conclusion, NEL is unlikely to offer significant advantages over ARAC, whilst FP may be effective if higher plasma levels can be delivered clinically. CLOF is marginally more effective than ARAC in B-lineage ALL but has a distinct resistance profile that may prove useful in combination with other compounds.

## Gene expression profiling of childhood pre-B acute lymphoblastic leukaemia in comparison with 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 with 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.

## Paediatric brain cancers

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

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

The molecular pathogenesis of primitive neuroectodermal tumours of the central nervous system (CNS-PNETs), the most common type of brain tumour affecting children, is poorly understood. Although 5-year survival rates have gradually improved to 50-70%, and the prognosis for those diagnosed with average risk CNS-PNETs is encouraging, the situation remains dismal for those with recurrent or metastatic disease. In addition, PNET survivors often face serious post treatment quality of life issues that can be devastating for both child and family.

The development of safer and more effective drugs and treatment strategies for children with PNETs has been severely hampered by the complex and relatively poorly understood molecular biology of PNETs. The brain tumour research program aims to address this problem and ultimately improve the outcome for paediatric brain tumour patients.

Chromosomal abnormalities are a common feature of PNET cells, including rearrangements, duplications, deletions, and amplifications. These and other data reflect the complexity of PNET biology and 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 our approach to identifying these genes, we have analysed chromosomal aberrations in a panel of PNET cell lines using cytogenetic analyses, representational difference analysis (RDA), and microsatellite mapping. This latter work was undertaken in collaboration with the Cancer Genome Project at the Sanger Centre, Cambridge, UK. More recently, in collaboration with Prof. Paul Meltzer from the

National Human Genome Institute at the National Institutes of Health in the USA we have assessed our PNET cell lines using array-CGH, a relatively high-resolution cytogenetic analysis technique. To further refine our focus to specific regions of the human genome, we have correlated our extensive cytogenetic data with the gene expression profiles of our five PNET cell lines and a panel of 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. Some of these genes have not previously been linked to PNET pathogenesis and represent promising new leads for ongoing study.

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

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

Our comprehensive molecular analysis of our panel of primary CNS-PNETs and CNS-PNET cell lines identified an oncogene, EZH2, and a tumour suppressor gene, FOXO1A, which were simultaneously deregulated in the majority of tumour specimens. These two genes function in pathways that regulate critical aspects of cell growth and differentiation. 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 over-expression or RNAi knockdown procedures. We anticipate that the NSC model system that we are developing 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.

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

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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.



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candidate

David J Holthouse, MBBS (Hon), BmedSci (Hon),  
PhD candidate

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

### ■ Research Support

Stewart Cattach

Reinete Orr

## Theses passed

Tina Carter PhD. A study of the INK4A/ARF  
and INK4B loci in childhood acute lymphoblastic  
leukaemia using quantitative real time polymerase  
chain reaction. UWA.

## External Committees

### ■ International

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

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

### ■ Regional

Ursula Kees. Cancer Council of Western Australia

## Invited Presentations

Peter Dallas. A human neural stem cell model  
for the study of the pathogenesis of primitive  
neuroectodermal tumours (PNETs). 6th Peter  
MacCallum Cancer Symposium, Melbourne,  
November 2005.

Ursula Kees. Microarray applications in haematology.  
Amgen Clinical Symposium, Sydney, February 2005.

Ursula Kees. Advances in childhood cancer: insights  
from genome-wide expression studies. CHUV,  
University of Lausanne, Switzerland, June 2005.

## Acknowledgments

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Children's Leukaemia and Cancer Research  
Foundation (Inc) is gratefully acknowledged. Our  
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the Management Committee of the Foundation.

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

Much of the work of the Division has revolved around the NH&MRC Asthma Program Grant. This is the fourth year of the five-year program and has been a year of preparation for the renewal application due early in 2006.

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 (henceforth 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 has continued and expanded its involvement in Children's Environmental Health. Peter Sly and Felicity Flack have been collaborating with the World Health Organization's Children's Environmental Health group for several years. We have almost completed the designation phase for becoming a WHO Collaborating Centre for Research on Children's Environmental Health. We expect this Centre to officially begin activities in 2006.

We have continued our CF research, including the program funded by 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 Dept of Respiratory Medicine at PMH. This three-year project is being conducted in collaboration with Drs. Philip Robinson and Colin Robertson from the Dept of Thoracic Medicine, Royal Children's Hospital, Melbourne.

## Asthma Program Grant

In broad summary, substantive achievements in the human studies within our Program include:

- identification of specific immunophenotype(s) in children associated with AHR;
- demonstration that parental smoking unmasks sensitivity to asthma susceptibility genes in their offspring, and for the first time pinpointing specific genetic targets for these Environmental Tobacco Smoke (ETS) effects;
- elucidation of the nature and sequelae of allergen "recognition" by immature T cells in infants;
- the role of DC maturation as a limiting factor in early programming and reactivation of T-cell memory;
- establishment of a unique model utilising primary isolates of airway epithelial cells from healthy, atopic and asthmatic children for investigations into airway injury and remodelling, and identification of associated drug targets;
- demonstration of the age-dependence of genetic mechanisms modulating susceptibility to airways inflammation, and age-related variations in asthma phenotypes;
- identification of novel genes encoding molecules involved in the early phase of reactivation of aeroallergen-specific Th2-memory cells;
- characterization of new environmental aeroallergens;
- identification of genetic and immunological mechanisms associated with acute severe asthma;
- development of new methods for measuring lung function in preschool-aged children.

Complementary findings of equivalent interest have arisen from our animal Program, including:

- identification of the triggering role of airway mucosal DC in the asthma late phase response, the *in situ* control of the function of these DC by locally recruited T-regulatory cells, and the interrelationship between these processes and the subsequent development of AHR;
- development of new techniques for measuring lung function in mice as young as 2 weeks old,

including measurement of absolute lung volumes, partitioning respiratory mechanics into components representing airway and lung parenchyma separately and tracking respiratory mechanics during lung inflation and deflation;

- development of new animal models, including neonatal allergen sensitization without the use of adjuvant, viral lower respiratory infections, intranasal sensitization without adjuvant to modified allergens or peptides, and novel models for immunotherapy.

The outcomes from the research include:

- Communication of results: 264 (unique) publications and 215 invitations to address major international and national scientific meetings. Four program CIs are listed in the ISI Web of Knowledge Scientist Citation Rankings most highly cited scientists in Clinical Medicine (Sly, Holt, LeSouef), Immunology (Sly, Holt, Thomas) or All Fields (Sly, Holt);
- Commercialisation of research: 9 patents filed and 2 spin-off companies formed;
- Translation of research: the launch of the first international trial of primary prevention of asthma via targeted immunointervention (ITN025AD) based on concepts developed by the Program team; introduction of routine measurements of lung function for preschool-aged children into the clinical management of children with asthma, cystic fibrosis and bronchopulmonary dysplasia; introduction of a clinical program for the early detection of lung disease for infants and young children with CF; introduction of the routine use of spacers to deliver asthma medication for children admitted to PMH with acute asthma; initiation of an internationally funded program for development of a new diagnostic/prognostic platform for improved phenotyping/treatment of atopic/asthmatic children.
- Public health impact: introduction of "NAPS", a state-wide, WA Department of Health department-funded, public health intervention campaign to reduce the prevalence of maternal smoking during pregnancy; application of research findings to tobacco control programs in conjunction with the WA Department of Health; influencing the international agenda on primary prevention of asthma and testing of new drugs in children (WHO Asthma/Allergy Prevention Guidelines; Nature Immunology Commentary).

## Respiratory Physiology

Alteration of airway tone in a mouse model of respiratory syncytial virus (RSV) infection.

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

The aim of this project was to determine the relationship between 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 was a three year project which formed the basis of Rachel Collins PhD research. Rachel completed her PhD at the end of 2005 and this project is now closed. Both 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, but only when the constrictor stimulus, Methacholine, was delivered via the airway lumen (by aerosol). 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. In 2005, the final limb of the study examined the potential roles of leukotrienes (LTs) and prostaglandins (PG) in RSV-induced hyperresponsiveness. Cysteinyl LTs (cysLT) and PGE<sub>2</sub> have been shown to be elevated in children with bronchiolitis and are both known to be potent bronchoconstrictors of smooth muscle. cysLT and PGE<sub>2</sub> were examined in the bronchoalveolar lavage fluid (BALF) collected from

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adult and weanling mice at 5, 7 and 21 days post inoculation with RSV. cysLT were elevated in both adults and weanling infected with RSV, peaking at 5 days post infection. PGE<sub>2</sub> was elevated in adults and weanlings at 7 days post infection. The increases were seen prior to inflammatory cell influx therefore the major source of these mediators is thought to be epithelial cells. These elevated levels of epithelial derived mediators indicate that epithelial mechanisms were the main determinant of the extreme airway hyperresponsiveness seen in this model of RSV infection.

## Physiological outcomes of influenza viral infection in mice.

Elizabeth Bozanich, Debra Turner, Rosa Gualano I, Gary Anderson<sup>1</sup>, Peter Sly. <sup>1</sup>University of Melbourne.

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. Previous studies in 2004 were conducted using BALB/c mice inoculated with influenza A/PR8 (H1N1). These studies yielded mixed results and were difficult to conduct as the strain of flu used was extremely vigorous in the mouse. In 2005 we changed flu strain and conducted a pilot study using influenza A/Mem71 (H3N1) flu obtained from our collaborators at Melbourne University. To date the data are very encouraging. The first limb of the study was designed to look at the acute effects of influenza infection. Animals were studied either 4 or 10 days after inoculation with either flu or media (controls). Flu infected mice showed heightened airway responsiveness

during the acute phase of the flu (day 4) with lung function returning towards control values by day 10. Unlike the studies with RSV, hyperresponsiveness was seen with both aerosolized and intravenous Methacholine. This study is ongoing.

## Assessment of respiratory mechanics in rodents.

Graeme Zosky, Alexander Larcombe, 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 and rats using a custom designed whole body plethysmograph. The measurement of lung volume using plethysmography in humans is complex but well established. It was first described by DuBois et al in 1956 (J Clin Invest 1956;35:322-326). Plethysmography involves placing a person in a chamber and having them take several breaths against a closed shutter using normal breathing. Changes of pressure in the box, brought about by compression and rarefaction of the gas within the chamber during inspiratory efforts, are related to changes in tidal volume. Plethysmography measures the volume of all the gas in the lungs, including any air trapped by closed or narrow airways, thereby providing a valuable method of measuring absolute lung volume and resting end expiratory lung volume, also known as functional residual capacity (FRC). Lung volume has been shown to alter with disease state, airway smooth muscle constriction, anaesthetic level, inflammation and a number of other factors. Assessment of lung volumes using whole body plethysmography in infants has assisted in the study of normal growth and development of pulmonary function and helped the study of therapeutic intervention in various respiratory diseases. Measurements of FRC have provided valuable information about alteration of lung function in the disease state. In our laboratory we routinely use rodents to assess the long and short term influences of allergen, virus and bacteria exposure, fibrosis and bronchoconstrictive agents on the lung, but to date we have not been able to measure lung volume in these murine models of airways disease. Prof Zoltan Hantos, our collaborator and co-worker from Szeged University in Hungary, has recently developed a whole body plethysmograph for the

mouse and a separate one for the rat. In 2005 studies in the mouse have proved very successful and we now aim to incorporate the technique into our routine lung function assessment. A pilot study in rats has also shown great promise. The ability to successfully measure lung volumes in the mouse and rat provides us with a valuable tool to enhance and improve our standard lung function measurements and provide valuable information on disease induced lung volume changes in our animal models.

#### Measurement of lung function using broadband forced oscillation.

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Cindy Thamrin, Kevin Finucane<sup>1</sup>, Bhajan Singh<sup>1</sup>, Zoltan Hantos, Peter Sly. <sup>1</sup> 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, which forms the basis of Cindy Thamrin's PhD, 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. We have 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 the past year, 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 HF resistance with lung volume were significantly

different compared to healthy age-matched subjects. Mathematical modeling showed that these changes to HF FOT parameters were consistent with an alteration to airway wall dimensions and damping properties. Cindy completed this project in 2005 with the submission of her PhD to The University of Western Australia in late December.

#### Murine models of allergic airways inflammation.

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Graeme Zosky, Elizabeth Bozanich, Alexander Larcombe, Olivia White, 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 work encompasses two main limbs, firstly to examine allergen induced airway and lung responses in a commonly used mouse and rat model of asthma. The aim of the project was to determine whether rodents sensitised with a traditional regime of systemic allergen and alum show an allergen-induced early and late phase response similar to that seen in human asthmatics. Consistent early phase responses were seen by 10mins in sensitised BALB/c mice, but no late phase bronchoconstriction was seen by 8 hours post allergen exposure. Work is ongoing in 2006 to determine if responses will be seen further out, ie 12 or 24hrs after allergen. In rats, preliminary data shows that allergen-induced late phase responses, measured as alterations in specific airway resistance, are present around 2-4hrs. Early responses have yet to be studied in the rat. The second limb of this work involves the development of a model of asthma that involves exposure to the sensitizing allergen early in life. In 2005 we established a model of allergic sensitisation in neonatal mice; a situation which more closely mimics the sensitisation of the immature immune system in humans. To date the study has produced some very exciting results with evidence to show that sensitisation to allergen on the day of birth followed by one boost at weaning (4 weeks of age) can result in heightened airway hyperresponsiveness as an adult (at 8 weeks of age). This shows great promise as a model of neonatal sensitisation.

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Interface of T regulatory cells, physiology and cytokines in a murine model of asthma.

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Jennifer Burchell, Debra Turner, Phil Stumbles, Matt Wikstrom, Peter Sly.

Many studies have confirmed the central role that CD4+ T helper 2 (Th2) cells play in the development of the allergic asthma. However, the precise role that these cells play in mediating the clinical symptoms of allergic asthma, including airways hyperresponsiveness (AHR) and airflow limitation remains unclear. Furthermore, there is evidence to suggest that CD4+ T cells, as well as being initiators of disease via polarization to the Th2 phenotype, may also act at later timepoints to downregulate allergen responses via an alternative differentiation pathway resulting in regulatory CD4+ T cell (Treg) populations. Again, the mechanisms controlling this process remain poorly understood. Using experimental mouse models of allergic asthma that allow precise tracking of allergen-specific CD4+ T cell responses *in vivo*, we plan to address the hypothesis that CD4+ T cells play a dual role in both initiating (as Th2 cells) and regulating (as Treg cells) the allergic asthmatic response. We further hypothesize that these dual roles will be temporally regulated during the course of disease through the co-ordinated production of cytokines and interactions with environmental stimuli such as bacterial-derived immune-modifying agents. To our knowledge, this will be the first *in vivo* study to accurately describe the events leading to the induction of CD4+ T cell mediated allergic airways disease and allergic asthma from the time of initial allergen exposure to the onset of clinical symptoms in the conducting airways. Analysis of the differentiation of the major subsets of CD4+ T cells (Th1, Th2, T reg) during disease development and the impact of environmental stimuli on the clinical outcomes of this process will provide a significantly improved level of understanding of the underlying pathogenesis of this disease and identify novel pathways for development of intervention strategies. This project forms the basis of Jennifer Burchell's three year PhD research. In 2005, a model of allergen induced physiological tolerance was established. This model involved sensitizing BALB/c mice to the allergen ovalbumin (OVA) and subsequently exposing them to multiple OVA aerosols. Airway hyperresponsiveness was induced

after 1 OVA aerosol and was suppressed (ie tolerance induced) after 16 aerosols. Inflammatory cell influx to the airways and parenchyma and immunoglobulins (IgE and IgG1) followed a similar pattern of enhancement after 1 aerosol and suppression after multiple aerosols. This tolerance model will be used in 2006 to examine the role of T regulatory cells in mediating airway hyperresponsiveness.

The regulatory role of IL-17 and IL-23 in a murine model of airway reactivity.

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Debra Turner, Graeme Zosky, Alexander Larcombe, Gary Anderson<sup>1</sup>, Anders Linden<sup>2</sup>, Peter Sly. University of Melbourne<sup>1</sup>, University of Gothenburg<sup>2</sup>.

IL-17 (also named IL-17A) was cloned more than ten years ago and six IL-17 family members (A-F) have subsequently been described. An increasing body of evidence suggests that IL-17 family members play an active role in inflammatory disease, autoimmune diseases and cancer. Of particular interest is that the production and release of IL-17 appears to orchestrate neutrophil activity in the lungs. IL-17A and IL-17F have strong neutrophil-mobilising properties and recently IL-17A has been found to be increased in mild asthma. In animal models, the literature is limited but indicates that endogenous IL-17A is involved in mediating allergen-induced AHR to methacholine (MCh) in mice. However this study was conducted using an unrestrained plethysmograph system, which has recently been shown to be incapable of accurately determining respiratory physiology under conditions such as bronchoconstriction. Therefore, the physiological implications of IL-17 have yet to be fully elucidated. IL-17A and IL-17F are regulated upstream by IL-23. To date, very little work has been published looking at the regulatory effects of IL-23 on IL-17 production and subsequent neutrophil recruitment. Thus, in collaboration with Dr Gary Anderson (University of Melbourne) and Anders Linden (University of Gothenburg, Sweden) who has written several reviews on IL-17 we are well placed to examine the physiological consequences of administering exogenous IL-23 and IL-17 to mice. This work is significant in that determining a role for IL-23 and IL-17 in AHR places these cytokines and their receptors as potential targets for future

therapeutic pharmacological intervention. We commenced this project in August of 2005 during a visit from our Swedish collaborator Anders Linden. The first phase of the project is to investigate the regulatory effect of exogenous IL-23 in allergen sensitised and challenged mice. Two strains of mice are being used, BALB/c and 129/Sv mice. To date the data is preliminary and inconclusive. The study is ongoing.

## Internal collaborations

Throughout 2005 we have been involved in several ongoing collaborative research projects within the Telethon ICHR. These projects are written up in greater detail elsewhere within this annual report by our collaborators, noted in parenthesis below. In brief we have assessed airway and tissue mechanics in the following collaborative studies;

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

## Clinical Asthma Studies

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

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

263 children at genetic risk of atopy were recruited in 1996-98 to participate in this prospective birth cohort which was set up to investigate the role of early respiratory infections on the maturation of the immune system and subsequent development of atopic disease. The first phase of the study was completed in August 2003 and plans are underway for a 10-year old follow-up visit which will commence in July 2006. This visit will identify children who have been diagnosed with asthma since the last visit as well as persistent asthmatics. Our understanding of the development of the immune system and factors affecting immune maturation will be further enhanced by data collected during this visit. The commitment and contribution made by the study children and their families throughout the study is acknowledged.

### HPA axis responsiveness in adolescents

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Lisha van Reyk, Marie Deverell, Sven Silburn, Nick de Klerk, Merci MH Kusel & Peter D Sly

The western world has seen a dramatic increase in the prevalence of asthma in the past few decades, and while there is no doubt that factors associated with the "western way of life" are involved, the precise cause of the increase remains elusive. As well as environmental and physical factors, psychosocial factors may play a part.

Epidemiological studies have found associations between stress in early life and atopic diseases such as asthma. One possible link between psychological stress and physical disease may involve the Hypothalamic-Pituitary-Adrenal (HPA) axis. Evidence suggests that an appropriate HPA-axis response to stressful stimuli is important in the development and control of the immune system, with an altered HPA axis response being associated with immune diseases such as rheumatoid arthritis and atopy.

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This study has developed and validated the CO<sub>2</sub> inhalation test as a suitable method for assessing HPA axis responsiveness to stress in children. The test is very well tolerated and results in a significant increase in salivary cortisol levels.

This test has been applied to children from the West Australian Pregnancy cohort with 1470 children assessed to date.

Preliminary analysis show associations between anxiety and HPA responsiveness with some gender differences being identified. Data collection will be completed in 2006 and early life factors as well as asthma and atopic status of the individual considered in the analyses.

## The Role of viral lower respiratory infections in allergy and asthma

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

A proportion of infants hospitalised with wheezing illnesses continue to have recurrent episodes of wheeze and become asthmatics in later childhood. This study commenced in 2001 to determine how wheezy illnesses caused by RSV/Parainfluenza alter lung function and to assess associations between immunological status, infection severity and eventual atopic outcome. Of the original 105 infants recruited, 86.7% have been followed up till 18 months of age, with 36 (34.3%) of the children undergoing infant lung function testing under sedation. Due to technicalities encountered in sedating the children at this visit, the remainder of the children in the cohort were not tested, and instead lung function using FOT (Forced Oscillation Technique) method was used. Preschool lung function testing using FOT is performed at 3 years of age, with 29 children so far having been tested. Further follow up of the children will continue on an annual basis till they reach 5 years of age.

Using immunoprophylaxis in the primary prevention of allergic disease.

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Peter D Sly, Patrick G Holt, Richard Loh, Carlie Dunford & Cathy Pienaar

One of the major risk factors for asthma and allergies in children is to come from a family that has asthma and/or allergies. Allergies that start early in life are likely to be more severe and are more likely to be associated with asthma that does not go away as the child gets older. So while allergies are not the only cause of childhood asthma, prevention of allergies may help prevent asthma.

In this study, we wish to determine whether we can prevent the development of allergy and asthma in high-risk children by using oral mucosal immunoprophylaxis (OMIP), which is the repeated exposure of the oral mucosa to high-dose allergen to prevent allergic sensitization to the allergen. We will conduct a double-blind, randomized, placebo-controlled trial in which children will receive drops of either allergen mix (containing house dust mite, timothy grass and cat) or placebo once a day for 12 months. The children will be followed for 3 years after treatment to determine whether allergies and asthma can be prevented using this method.

Globally, 200 children between the ages of 18 and 30 months will be recruited at one of five centres – Perth, Melbourne, New York, Stockholm and Berlin beginning in March 2006. The study involves allergy and pulmonary function tests, which includes baseline lung function and bronchodilator response.

## Infant and Preschool Lung function studies

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

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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 with

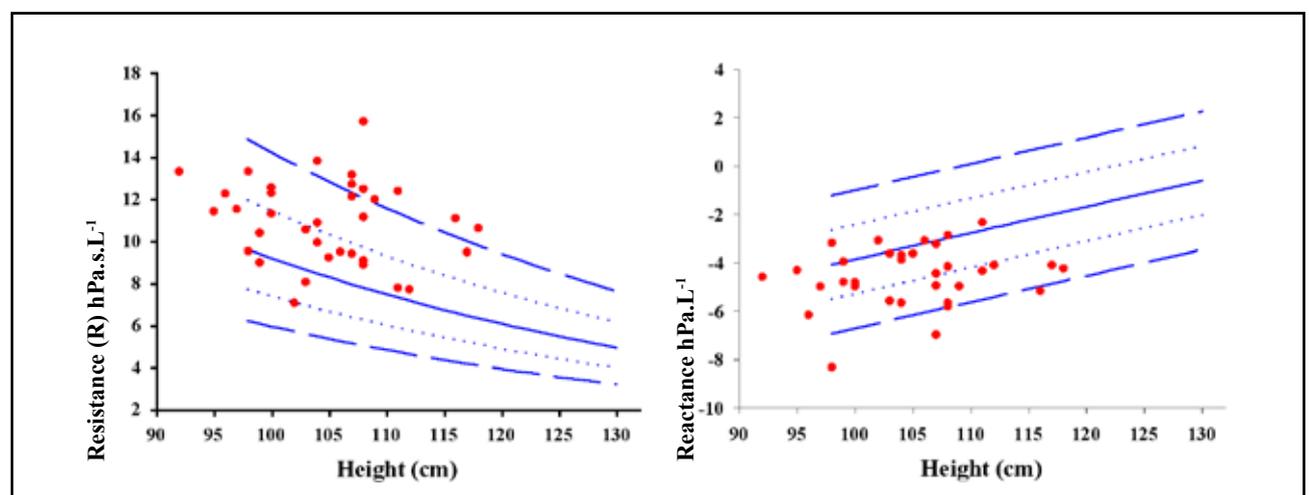
that seen in healthy preschoolers. Children with BPD had abnormal lung function, both resistance and reactance (see figure below) despite being asymptomatic when tested. These abnormalities were corrected by inhaled bronchodilator. The main predictor of abnormal lung function was the number of days of 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.

#### 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, 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

S Brennan, K Winfield, PD Sly, SM Stick, GL Hall, P. Robinson<sup>1</sup>, C. Robertson<sup>1</sup>, S. Thonell. <sup>1</sup> Royal Children's Hospital, Melbourne

In 2005 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 a three hundred and thirty broncho-alveolar lavage fluid samples have been collected from 100 children with CF. Inflammation is evident in virtually all of the lavage fluids collected, even in the very young infants (from four weeks of age) with no apparent clinical symptoms or infection.
- It appears that once acquired, inflammation consistently tracks with infection.
- The level of acquisition of *Staphylococcus* and *Haemophilus* is lower in this cohort than compared with other national CF centres for the same age group. This may be a consequence of the prophylactic antibiotic policy in the WA paediatric clinic.

- Whilst there appears to be no difference in the age of acquisition in *Pseudomonas* in our clinic compared with the other national CF centers, the lavage program has demonstrated some success at eradicating *Pseudomonas aeruginosa* in young children with CF.

We are currently constructing a working database for the analysis of this data. Numerous collaborations (national and international) have resulted from this ongoing study.

### Inflammation in cystic fibrosis: Friend or Foe?

PD Sly, S Brennan, K. Winfield.

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

The study involves the recruitment of children with CF and children with no history of lung disease for our control population. We have recruited children for this study from both 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 trialed in the CF community locally and nationally, will influence

these levels.

This study received funding from the National Cystic Fibrosis Association for 2002 and the first journal article outlining the validation of the technique and describing the effect of age in a non-CF pediatric population has been written by Ms Kaye Winfield and accepted for publication in the *Annals of Clinical Biochemistry*. Further submissions for journals resulting from these studies are currently being compiled.

Several collaborations have 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.
3. Collaboration with Dr. Yvonne Belisis, Westmead children's hospital investigating the effect of reflux on markers of lung inflammation.

#### Macrolide therapy for CF lung disease: evaluation of mechanism of action

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PD Sly, S Brennan, K. Winfield, G. Ryan<sup>1</sup>, P. Robinson<sup>2</sup>, Bruce Rubin<sup>3</sup>. <sup>1</sup>Sir Charles Gairdner Hospital, Perth; <sup>2</sup>Royal Children's Hospital, Melbourne; <sup>3</sup>Wake Forrest University, USA

In collaboration with Abbott USA and Abbott Australasia we are studying the use of the macrolide antibiotic, clarithromycin in the patients with cystic fibrosis.

Macrolides are a class of antibiotics that are not

routinely used for their antimicrobial properties in cystic fibrosis. Clarithromycin or placebo was given to 90 patients for 12 months in addition to their regular therapy. Clarithromycin is being tested for its 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 release of the final report is pending final analysis on quality of life.

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

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S. Brennan, J. Upham, M. Wikstrom, PD Sly, S. 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 bronchoalveolar lavage fluid of children with CF. Children with CF have recurrent infections, which are often difficult to clear and we hypothesise that one reason for this is that there is a dysregulation of the "surveillance" system, which involves the antigen presenting cells in the airways- the dendritic cells and macrophages. With the assistance of the respiratory fellows in respiratory Medicine (Dr Tonia Douglas, Andres Shultz and Paul McNamara) 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. In addition we have investigated the expression and activity of TLR2 and TLR4 receptors on monocytes in the blood and on macrophages in the lung.

This study began in late 2003, and received funding from the Australian cystic Fibrosis Research Trust for 2004. The initial findings of this study are being prepared for publication and some of this work has been used to form the basis of an NHMRC application for 2007.

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

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T. Douglas, S. Brennan, PD Sly.

This pilot study aims to investigate the value of *Pseudomonas aeruginosa* antibody levels as markers of early respiratory infection with *Pseudomonas aeruginosa* and response to treatment in young children with cystic fibrosis (CF). *Pseudomonas aeruginosa* (Ps a) is a primary CF pathogen that accelerates lung disease and increases mortality. Initial "intermittent" infection with pseudomonas is potentially treatable if detected before chronic infection is established. Currently detecting early respiratory infection reliably in young children with CF requires bronchoscopy under general anaesthesia. Less invasive methods of sampling respiratory secretions in children such as oropharyngeal swabs are insensitive and do not reflect lower respiratory bacteria accurately. Infection with Ps a stimulates the production of antibodies to Ps a proteins and toxins that are detectable in the serum. Levels of these antibodies in children were found to be sensitive markers of early *Pseudomonas* infection in the lungs, and response to anti-pseudomonas treatment, they may be useful in management of lung disease and may reduce the need for more invasive surveillance. However, studies investigating the potential of these markers in young children are scarce. The Respiratory Department at PMH has an established bronchoscopy program for all children in WA with CF and offers each child an annual bronchoscopy and bronchial lavage (washings) until around the age of 6 years. This unique program permits the study and treatment of respiratory infection and inflammation in children too young to expectorate or cooperate with conventional methods of lung surveillance. The potential of antibodies to *Pseudomonas* as markers of respiratory infection can therefore be assessed and, in this study, compared with the "gold standard" of bronchial lavage throughout early childhood. Data from this study will determine whether a larger prospective study is warranted and the sample size required.

This pilot study was funded by the Princess

Margaret Hospital seeding grants scheme, and now forms the basis of an honours project to be conducted during 2006.

## Other research

Promoting assent: involving children in the decision-making process in therapeutic clinical trials.

Angela Alessandri, Linda Kristjanson<sup>1</sup>, Peter D Sly.  
<sup>1</sup>Edith Cowan University.

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

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

Jackie M Cesareo<sup>1</sup>, Davina French<sup>1</sup>, Sven Silburn, Peter D Sly. <sup>1</sup>Department of Psychology, UWA

This project is using longitudinal data collected from the Raine cohort to examine the interactions between psychosocial stress and asthma in children. Specifically, the role stress and family functioning can play in the induction of asthma is a major focus. We are also investigating whether 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.

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Tonia Douglas MBChB MRCPCH

Felicity S Flack PhD

K.E (Bill) Finucane (Emeritus Professor)

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

Merci Kusel MBBS PhD

Alex Larcombe (PhD)

Hilary Patterson BE (Hons) BSc

Cathy Pienaar BSc (Nursing) MSc (Med)

Jane Pillow MBBS, FRACP, PhD

Nina Sturges BSc(Hons)

Debra J Turner PhD

Kanokporn Udomittipong MD C.Paed

Olivia White BSc(Hons)

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

Jennifer Burchell 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.

Rachel Collins (PhD thesis): Dysregulation of airway  
function following respiratory syncytial virus infection.

## Awards

Peter Sly - Thoracic Society of Australia and New  
Zealand, 2005 Research Medal

Peter Sly- Dr. H Paramesh Oration, Indian Academy  
of Paediatrics, 2005

Graeme Zosky, QANTAS Young Investigator Award

Cindy Thamrin – John Read prize for Physiological  
Research (Australian Lung Foundation & Thoracic  
Society of Australia and New Zealand), awarded at  
the TSANZ conference, Perth, March 2005.

# Division of Clinical Sciences

## 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. TSANZ (WA Branch) Executive Committee

R Collins. TSANZ (WA Branch) Associates Subcommittee.

Debra Turner. Board of Directors, Scitech, Western Australia

## Invited Presentations

The developing burden of asthma in Southeast Asia and China. RJ005 Child Asthma and Allergy Diseases Forum, Shanghai, May 2005

Defining atopic asthma in preschool children. RJ005 Child Asthma and Allergy Diseases Forum, Shanghai, May 2005

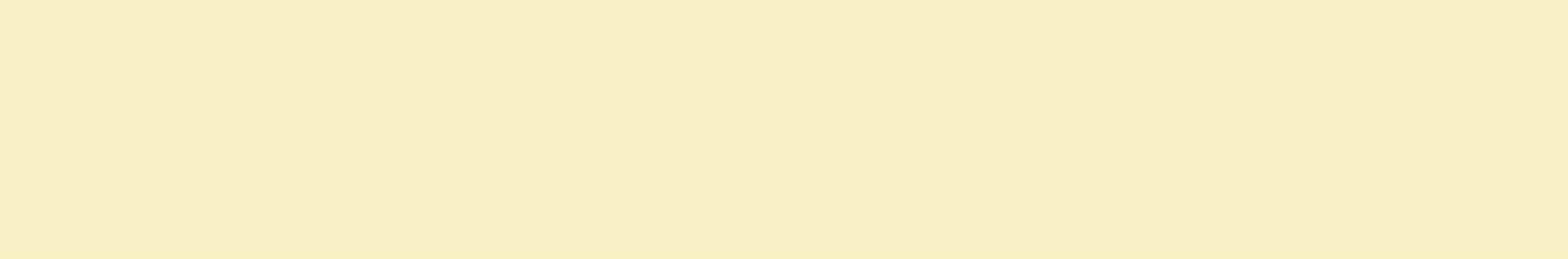
Impact of Environmental Pollutants on Childhood Asthma, Pacific Basin Consortium, Hawaii, Sept 2005

Environmental Effects on Respiratory Diseases. Respicon 2005, Bangalore, India, Sept 2005

Respiratory Disease in Children, Rotary Club of Valentano, Italy, Sept 2005

Role of Macrolides in Patients with Cystic Fibrosis - Who Should Get Them and for How Long? Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Perth 2005

Sly PD. Asthma Researcher – Bringing research into your clinical setting. Audiological Society of Australia, Annual Continuing Professional Development Day 2005



# Division of Molecular Biotechnology

Research in the Division of Molecular Biotechnology has focussed on understanding the mechanisms of inflammation and allergy and developing new methods to treat disorders produced or exacerbated by allergy and inflammation.

House dust mite allergy and its role in asthma has been investigated by the analysis of the immune response to the allergens. The difference in the type of immune response induced by highly allergenic proteins and poorly or non-allergenic proteins has been investigated as well as the differences in the responses of severely or mildly asthmatic people. The recent study of the responses of children admitted to the emergency department for asthma has shown that highly asthmatic children are allergic to the same spectrum of allergens as children with less severe allergy but show a major change manifest by decreased IgG antibody titres. As well as demonstrating this major difference the study has shown that a small cocktail of allergens could equally be used for immunotherapy to treat the severe asthmatic patients as well as mildly asthmatic children. The ongoing studies of experimental immunotherapy in mice are aimed at developing or discovering methods to treat allergic disease induced by mixtures of allergens. Cat allergy is similarly being studied to elucidate the interplay between responses to different allergens in health, disease and in immunotherapy. The production of and characterisation of recombinant allergens is a major undertaking that underpins the measurement of responses to defined antigens and development of potential therapeutic agents,

The inflammation group has analysed the

effects of ultraviolet (UV) light exposure on immune responses and at a more fundamental level analysed the molecular regulation of inflammatory cytokine responses in human macrophages and monocytes. The discovery by the group that UV irradiation induces regulatory T cells to exert immunosuppressive effects throughout the body has many practical consequences as well as providing an excellent model for studying the activity of the regulatory cells. The research on cytokine regulation in inflammation has successfully employed 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 signalling (SOCS) genes and the STAT family of transcription factors. The effects are different to those reported in the mouse models. Studies are on human cells thus highly relevant. A comparison of the biochemical pathways used by humans and mice function could help uncover the core functions of these regulators.

## Allergy

Antibody responses to house dust mite allergens by children admitted to the Emergency department.

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

A quantitative solid phase DELFIA (dissociation enhanced lanthanide fluorescence immunoassay) has previously been developed to provide absolute measurements of IgE, IgG1 and IgG4 antibody responses to allergens. The titres of antibodies to a 9-allergen panel consisting of Der p 1, 2, 3, 4, 5, 7, 8, 10 and 20 has been used to compare the

IgE binding by sera from children recruited from community-based cohorts with that of children recruited from the emergency department of Princess Margaret Hospital. The aim was to ascertain the characteristics of the responses of children with severe asthma and thus help identify the most important allergens to include in formulations for new types of immunotherapy. IgE antibody responses to the major Der p 1 and Der p 2 allergens and to the mid-range Der p 4, 5 and 7 allergens were high in children attending the emergency department but not significantly higher than the titres in sera from the community-based recruits. The responses to Der p 3, 8, 10 and 20 were low. Children with severe disease therefore did not show a higher or more complex response. IgG1 and IgG4 antibodies could readily be detected to the major Der p 1 and Der p 2 allergens and to a lesser degree to the mid-range allergens. The IgG antibodies were however only found in sera from allergic subjects and were more prominent in children than adults. A very significant reduction in the prevalence and the titres of the IgE was found in the sera from the emergency department admissions. The decreased IgG is thus a marker for severe disease or in the case of the adults a long-lasting allergic response. The production of both IgG1 and IgG4 and the restriction to allergic subjects shows that allergy is associated with both Th1 and Th2 type responses.

#### T-regulatory responses in house dust mite allergy.

B. J. Hales, N.N.R. Chu, L. A. Hazell, W. R. Thomas

The FOXP3 is a transcription factor produced by activated regulatory T cells. To examine the possible role of the regulatory T cells in allergic sensitisation the FOXP3 transcription induced by the stimulation of peripheral blood mononuclear cells by the house dust mite allergens Der p 1, Der p 2 and Der p 7 was examined as well as by the P6 antigen of *Haemophilus influenzae*. The major allergens induced FOXP3 transcription but the responses were highest to the major allergens and highest in allergic compared to house dust mite non-allergic subjects. The mid-range Der p 7 allergens induced higher levels of FOXP3 transcription in allergic subjects with the level being correlated with the IgE titre of the donor. The T-regulatory response

thus appears to be more of a feedback mechanism induced by allergic sensitisation rather than a response that prevents sensitisation in non-allergic subjects. The FOXP3 was shown to be produced by CD25 positive CD4 positive T cells in keeping with the known surface phenotype of regulatory cells.

#### The chitinase allergens of *Dermatophagoides pteronyssinus*.

S. E. O' Neill, W.R. Thomas, L. A. Hazell, T. K. Heinrich

The cloning of the chitinase and chitinase-like Der p 15 and Der p 18 allergens of the mite *Dermatophagoides pteronyssinus* has previously been reported. The importance of these allergens has been investigated because dogs have been reported to make their major IgE responses to the homologous allergen of the related mite *D. farinae*. The allergens could either be important allergens of humans or provide an interesting inter-species comparison. The Der p 15 and 18 cDNA were expressed in inclusion bodies of *Escherichia coli* and the resulting polypeptides were solubilized and renatured. The Der p 15 polypeptide bound IgE in 70% of sera from mite-allergic subjects and the Der p 18 in 63%. This 60-70% is higher than the prevalence generally reported for house dust allergens other than the major Der p 1 and Der p 2 allergens and the tropomyosin and paramyosin allergens in South East Asian countries. This and the high reactivity reported for dogs indicates the need for further study especially the isolation of the correctly folded natural allergens. The two chitinase proteins were not antigenically cross-reactive.

#### Cloning of uncharacterised house dust mite allergens

TK Heinrich A. Kutasi, LA Hazell BJ Hales WR Thomas in collaboration with Dr Seiji Kawamoto, Ph.D. Professor. Kazuhisa Ono, Hiroshima and Dr Debbie Holt, Queensland.

Several allergens which have reported as being important in other countries, particularly South East Asia, are being investigated. As shown for tropomyosin the reactivity of allergens can vary in different regions. cDNA encoding the complete paramyosin Der p 11 allergen has been cloned

# Division of Molecular Biotechnology

and because the whole allergen is unstable, fragments representing polypeptides reported to be reactive with IgE have been expressed in *E. coli* for serological studies. Likewise cDNA encoding the allergen encoding the fatty acid binding protein Der p 13 (homologous to Blo t 13 from *Blomia tropicalis*) was cloned so the reactivity can be tested to a pyroglyphid mite in with sera from people living in a temperate environment. A previously unreported allergen designated MagI 33 has been cloned from *Dermatophagoides farinae* in Japan by Ono and Kawamoto and reported to show high IgE binding activity. The *D. pteronyssinus* equivalent of this YjgF or protein UKI 14 like protein was cloned and it was readily expressed in *Escherichia coli*. The IgE binding will be investigated.

## Genetic polymorphisms of major dust mite allergens

W. R. Thomas with S. Piboonpocanun, M. Malainual, O. Jirapongsananuruk, P. Vichyanond, Mahidol University, Bangkok

Sequences of the major group 1 and 2 allergens obtained from house mites isolated from homes in Bangkok were analysed with respect to sequences found elsewhere in the world. The sequences included the Der p 1 and 2 allergens from *Dermatophagoides pteronyssinus* and the Der f 1 and 2 allergens from *Dermatophagoides farinae*. The data from the Der p 1 confirmed the prevalent polymorphism of this allergen. As well as the presence of sporadic variations there were substitutions in residues that had previous been shown to be polymorphic. The identification of these mutational hot spots could be useful for the genetic engineering of this allergen to produce hypoallergenic constructs. The result of the Der p 2 analysis confirmed previous results showing the presence of two evolutionary lineages of this allergen. The lineage represented by the prototype allergen Der p 2.0101 was however poorly represented in Thailand and the Der p 2.0101 itself was not found. Since the polymorphic lineage represented by Der p 2.0104 is known to be more allergenic than Der p 2.1010 the use of this polymorphism has been recommended for the production of a universal recombinant Der p 2. The *D. farinae* sequences have not been well studied before and showed interesting results. Like

the Der p 2 allergens two evolutionary lineages of Der f 2 were identified. The positions of 5 amino acid residues that varied were however completely different to the position of Der p 2 occurring in a different region of the tertiary structure. Surprisingly the Der f 1 showed very little polymorphism even though the same mites showed the frequent genetic variation of Der f 2. These results here have identified sequences that have been recommended for the production of universal recombinant allergens and identified sequence changes that could affect the allergenicity of the different allergens and variations of mites in different geographical regions.

## Cloning and testing of novel cat allergens

SE O'Neil, NNR Chu, LA Hazell, W. Smith and BJ Hales

The study of cat allergens has primarily been limited to proteins detected in cat dander and cat skin. The salivary and other mucosal glands are however known to be important sources of IgE binding proteins. In a project designed to validate the use of the known major Fel d 1 allergen for immunotherapy, the possible importance of other allergens is being investigated. cDNA libraries prepared from the mandibular, von Ebner and anal gland of the cat have been screened for IgE binding proteins with sera from people allergic to cats. Clones producing IgE binding proteins have been identified as encoding the cat IgG heavy chain, a proline rich acidic protein, an MHC-related glycoprotein and a latherin-like molecule that was similar to known horse allergens. The prevalence of IgE binding to these clones is now being determined. The previously identified salivary lipocalin (Fel d 4) and the S100A12 IgE binding protein are being tested for their ability to induce T-cell cytokine responses along with the cat albumin (Fel d 2) and cystatin (Fel d 3) described by others. To date the Fel d 1 has been shown to induce Th2 cytokines in allergic subjects with only sporadic responses to the other allergens.

## Allergen Mimotopes

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TK Heinrich, CM Hall, LA Hazell BJ Hales WR Thomas

Antibodies to the major house dust mite and cat allergens have been used as immunoabsorbents for panning phage display libraries for peptides that mimic the antibody epitope. The libraries either displayed random peptides from standard M13 combinatorial oligonucleotide libraries or displayed peptides from a library made from randomly fragmented genomes of a panel of 25 phylogenetically diverse bacteria. Two of the five monoclonal antibodies enriched phage. The peptides isolated by the 10B2 anti-Der p 2 monoclonal antibody had a well-defined consensus sequence that resembled a sequence found in the original Der p 2 molecule. The monoclonal antibody was shown to block the binding of another monoclonal antibody known to bind in the region and to be unable to bind to the related Der f 2 allergen that showed a variation in one of the conserved residues of the consensus sequence. Fusion polypeptides of the natural 10B2 epitope (amino acids 69-82) and the glutathione-S-transferase of *Schistosoma japonica* could immunise mice to induce anti-Der p 2 antibodies but the responses were variable and fluid phase competitions could not be achieved indicating a low affinity. Some of the mimotopes showed higher antibody binding than the natural epitopes and when used for immunisation one these induced consistent responses and antibody that could be competed with natural Der p 2 showing high affinity. It is therefore possible to improve epitope-specific immunisation with the use of a selected mimotope. Mimotopes that bind to a Fel d 1 monoclonal antibody have also been isolated. A less defined stringent consensus sequence was apparent than that for the Der p 2 mimotope and unlike the Der p 2 there was no similarity to a sequence found in the natural allergen, showing a true structural mimic. None of the mimotopes isolated from the fragmented genomic libraries were part of a natural open reading frame of the bacteria used to produce the library, a property that could have stabilised their structure.

## Desensitisation of allergic responses to cysteine protease antigens.

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

The major Der p 1 allergen of the house dust mite is a cysteine protease. The biochemically similar, but commercially available papain allergen has been used to study allergic sensitisation and desensitisation therapy for this type of allergen. The model is particularly relevant because the papain can induce IgE antibody and lung inflammatory responses following intranasal sensitisation. Previous studies have demonstrated the high success of the subcutaneous protocols for vaccination. In a protocol of desensitisation it has now been shown that subcutaneous, sublingual and oral administration are all able to decrease the IgE antibody response. The sublingual and oral regimens show for the first time that mucosal tolerance can be used to inhibit responses induced at the respiratory mucosa. This is a promising model for optimising mucosal methods of desensitisation that could be less traumatic for clinical use. Experiments with a related cysteine protease bromelain have shown the specificity of the desensitisation. The regimen however did not reduce the cellular infiltration of sensitised mice so further protocols need to be tested, one being low dose administration that is more effective at reducing IgE. Chronic exposure of mice to papain leads to continued IgE antibody, bronchial wall thickening, and epithelial damage and collagen deposition. On challenge chronically exposed mice develop a combined eosinophilic and neutrophilic infiltrate compared to the purely eosinophilic inflammation found after shorter-term sensitisation.

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

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S.B. See and W R Thomas

A model is being established to examine the reciprocal interactions of allergic responses to aeroallergen and the respiratory infection with the natural opportunistic pathogen *Pasteurella pneumotropica*. This follows the observations that asthmatics show divergent immune responses to a similar bacterial infection with *Haemophilus influenzae* (which is not a natural infection of mice).

# Division of Molecular Biotechnology

In order to measure the immune responses to the bacteria a PCR strategy has been used to clone DNA encoding known conserved outer membrane proteins. The sequence of the related *P. multocida* and *H. influenzae* has been used to develop primers. The protein P6 of *P. pneumotropica* has been produced in *Escherichia coli* as a hexahistidine fusion protein containing almost all the natural sequence and shown to react with serum from mice immunised with whole *P. pneumotropica*. Other antigens D15 and P26 are similarly being prepared. A ribosomal DNA PCR test has been developed to use to detect and measure the infection. Mice experimentally infected by intranasal administration of *P. pneumotropica* have been shown to develop pneumonia in a dose-dependent fashion and this has been confirmed by bacteriological culture and PCR.

## Inflammation

### Immunomodulatory effects in mice of UVB radiation

PH Hart, JJ Finlay-Jones, S Gorman, J Tan

UVB immunomodulatory effects have been implicated not only in skin cancer development but also in the initiation and progression of autoimmune and infectious diseases in experimental animals. UV rays cannot penetrate beyond the outermost layer of skin. In our studies, the effects of UVB on systemic immunomodulation are studied. The shaved dorsal skin of mice is irradiated whilst the ventral skin provides the site for antigen sensitisation several days later. The immunomodulatory effects of UVB result in reduced swelling of the ears when they are challenged by surface painting with the same antigen after a further five days. To better understand the molecular mechanisms involved, lymph node cells draining sites of UVB irradiation and/or antigen 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 antigens, we have not found any difference in the phenotype or function of these antigen presenting cells from control and UVB-irradiated mice. 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. We are seeking the phenotype and function of these regulatory cells. Are new regulatory T cells induced or are we measuring an accumulation of regulatory T cells in the lymph nodes draining UV-irradiated skin? Many experiments involve transfer of cells from a UVB-irradiated mouse into a naïve mouse subsequently challenged with antigen. Is regulatory T cell activation in donor mice sufficient for subsequent expression of activity in recipients? Alternatively do regulatory T cells require reactivation in the recipient mice, or in tissue culture? Thirdly, is T-Cell Receptor involvement important for their accumulation/activity? Is there any evidence that reduced immune responses to 'introduced' antigens is due to bystander suppression by UVB-associated T regulatory cells responding to UV-induced alteration of skin-derived antigens? These questions are being studied.

### Effect of UVB radiation on murine asthma models

PH Hart, J McGlade, WR Thomas, D Strickland, J Thomas, D Turner, G Zosky

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- $\gamma$ . The effect of a single exposure to UVB on two asthma models in mice is being 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 are UVB-irradiated on their shaved backs three days before sensitisation, resensitisation and challenge intranasally with the cysteine protease, papain. Serum papain-specific IgE levels are reduced by UVB exposure. In the second model, mice are irradiated on their shaved backs three days before sensitisation, and resensitisation, intraperitoneally with ovalbumin mixed with alum. The mice are subsequently challenged by aerosolised ovalbumin. Airways hyperreactivity is significantly reduced by exposure to UVB. The levels of inflammatory cytokines in lavage fluid are 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.

#### The receptor for cis-urocanic acid

PH Hart, E Woodward, CM Prele, JJ Finlay-Jones

Urocanic acid (UCA, deaminated histidine) is a molecule produced by the skin in the trans form. It is located superficially in the outmost layer of skin (stratum corneum) where it accounts for 0.5% dry weight. Upon UVB-irradiation, the trans form isomerizes to its more soluble cis configuration. Many studies have implicated UCA as an immune photoreceptor in skin for UVB, particularly as very little UVB radiation penetrates skin lower than the epidermis. Our past experiments support a role for cis-UCA in UVB-induced systemic immunomodulation; cis-urocanic acid injected subcutaneously not only reduces systemic suppression of contact hypersensitivity responses to trinitrochlorobenzene in mice, but a single intraperitoneal injection of 0.1 µg cis-UCA antibody 4 hours before UVB irradiation removes approximately 60% of the immunosuppression caused by UVB irradiation. The receptor for cis-UCA has remained elusive. We have been studying the receptor for cis-UCA on human monocytes as we know that these cells respond to cis-UCA by decreased production of tumour necrosis factor and increased production of prostaglandins. We have shown that the receptor for cis-UCA is not a serotonin receptor.

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

PH Hart, CM Prêle, 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 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, the number of cells expressing GFP is approximately 65% with significant GFP expressed per transduced cell. The viability of the cells is not compromised. We are particularly interested in the mechanisms by which monocytes/macrophages are activated and then how IL-4 and IL-10 suppress monocyte/macrophage inflammatory cytokine production. We have cloned the plasmids for wild type STAT 3 (a potentially important signalling molecule), a dominant negative (mutated) STAT 3, and SOCS1 and SOCS3 (molecules important in regulating cytokine production in mouse macrophages) into 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 1 regulates LPS activation whilst SOCS3 regulates the activation of STAT3 by interleukin-6. 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.

# Division of Molecular Biotechnology

## Staff and Students

### ■ Head of Division

Wayne R Thomas, PhD

### Allergy and Immunology Group

#### ■ Research Staff

Paula Cunningham

Claire Elliot

Belinda Hales

Lee Hazell

Tajana Heinrich

Angelika Kutasi

Leigh Pearce

### Inflammation Group

#### ■ Research Staff

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

Shelley Gorman BSc (Hons) PhD

Cecilia Prêle BSc (Hons) PhD

Jamie Tan BSc MSc

April Keith-Magee BSc MSc

#### ■ Postgraduate Students

Jacqueline McGlade BSc, PhD Candidate

Eleanor Woodward BSc, Hons Candidate

## Theses Passed

Eleanor Woodward, Hons I

Stephanie Gunn, PhD

Ingrid Laing, PhD

## Invited Presentations

W. R. Thomas. Environmental and therapeutic inhaled particles – effects on the foetus  
International Society for Aerosol Medication, Perth,

W. R. Thomas. Allergen derived peptides from bench to bedside. American Academy of Asthma, Allergy and Immunology, San Antonio, USA

W. R. Thomas. Clinical trials with recombinant allergens, American Academy of Asthma, Allergy and Immunology, San Antonio, USA

W. R. Thomas. What makes proteins allergenic?  
American Academy of Asthma, Allergy and Immunology, San Antonio, USA

W. R. Thomas. Australian and New Zealand Society Laboratory Animal Science. Allergy to Laboratory Animals, Perth

W. R. Thomas. Mite allergens. World Allergy Congress, Munich, Germany

W. R. Thomas. Cloning of the Der p 1 and Der p 2 allergens. House dust mite workshop, Bangkok, Thailand

W. R. Thomas Allergenic responses to house dust mite allergens. Allergy and Immunology Society of Thailand, Pattaya, Thailand

W. R. Thomas Allergen standardisation. Allergy and Immunology Society of Thailand. Pattaya, Thailand

## External Committees

W. R. Thomas NHMRC Peer review Advisory Committee

W. R. Thomas. Chairman of International Allergen Nomenclature Committee

PH Hart Member, Medical Advisory Board, Sylvia & Charles Viertel Charitable Foundation

PH Hart Member, NHMRC Research Fellowships Committee Peer Review Advisory Panel



# Division of Population Sciences

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 a multi-disciplinary team consisting of epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists.

Projects within the Division investigate a wide range of complex issues including low birth weight, behavioural and mental health problems, autism, obesity and infection. 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 as well as 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 2005 include:

Jan 2005 - Indigenous Capacity Building Grant (ICBG)

2005 saw the first full year of operation of the NHMRC-funded Indigenous Capacity Building Grant (ICBG). We have established a board of management, held two team workshops to assist in the planning and identification of study proposals and supervisors & mentors, professional development writing workshops, and had other opportunities for networking and to act as advocates for Indigenous health. Also of note was the successful identification and recruitment, in late 2005, of a suitable coordinator for the ICBG to aid in maximising the benefits of the grant for all involved.

March 2005 - ARC Linkage Grant

The ARC 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 a number of industry partners and 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, 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.

The Intellectual Property Agreement to enable the linkage of data between the

different jurisdictions has been agreed and signed by the State of WA and the University of Western Australia. This was signed off in March 2005.

Four PhD candidates were selected and commenced their candidature variously in July and August 2005. These four students are recipients of APAI Scholarships. Two PhD students (self funded) are also doing their PhDs on the ARC Linkage project. The candidates have developed their research proposals and submitted ethics approvals. They will commence their research once their data have been linked and they have complied with all requirements for release of data. Health and Education data linkage commenced in December 2005.

#### April 2005 - Western Australian Aboriginal Child Health Survey (WAACHS)

The Western Australian Aboriginal Child Health Survey (WAACHS) has been one of the largest and most comprehensive investigations into the health and well-being of over 5000 WA Aboriginal children in their families and communities. The survey was designed to build a store of knowledge from which preventive strategies can be developed to promote and maintain the healthy development and the social, emotional, academic, and vocational well-being of Aboriginal children.

In April 2005 the second volume of results on the social and emotional wellbeing of Aboriginal children and young people was launched. Findings from the second volume of results have been communicated and disseminated throughout the state with members of the WAACHS project visiting almost all of the regions in WA, including the Kimberley, Pilbara, Mid West, Goldfields,

South West and Perth metro.

Presentations were also delivered to the national Mental Health Services Conference for Australia and New Zealand in Adelaide, the National Adolescent Mental Health Conference in Melbourne and the Charles Darwin Symposium on Indigenous Health in Alice Springs.

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.

September 2005 - Perth researchers receive national suicide prevention awards

Suicide prevention researcher Kate Miller has been recognised for her innovative work in developing safe, effective online resources for young people. Kate, 24yrs of age, is a project officer with the Ministerial Council for Suicide Prevention at the Telethon Institute for Child Health Research.

Kate has developed a unique Internet resource targeted at young people who access suicide prevention information or support through the Internet. Kate also is responsible for the website for the Ministerial Council for Suicide Prevention and developed the ASPIRE (Australian Suicide Prevention Information Resource Exchange) website, supported by Woodside Energy.

Professor Sven Silburn, who Chairs the Ministerial Council for Suicide Prevention at the Institute, also received an Outstanding Contribution Award to acknowledge his major role in suicide prevention research in Australia.

The LiFe Awards are presented annually

# Division of Population Sciences

by Suicide Prevention Australia, a non-Government not-for-profit organisation committed to supporting the important initiatives undertaken by all those working in suicide prevention.

October 2005 - WA team uses baby tooth to solve mystery death

In October 2005, a team of Perth scientists used a keepsake baby tooth to help a Queensland couple solve the mystery of their 7-year-old daughter's death, 14 years after she died.

Staff from the Western Australian Institute for Medical Research (WAIMR), the Telethon Institute for Child Health Research (TICHR) and the Neurogenetics and Forensic laboratories within PathWest, combined to establish that the little girl had died from the devastating neurological disorder, Rett Syndrome.

Despite intensive investigation, the little girl's condition went undiagnosed by doctors all through her life, so the fact that the cause of her illness and death was finally pinpointed, gave the family the information they needed to understand what had happened.

The group was able to make the diagnosis after carrying out a gene test on DNA extracted from the baby tooth. A paper outlining the effort has just been published in the international medical journal, *The Lancet*.

The Australian Rett Syndrome Study is a nation-wide study of Rett syndrome that is directed from the Telethon Institute for Child Health Research. It involves a collaboration of centres across Australia with the common goal of being able to

provide accurate information about the progression of the disorder and about how it can best be managed. The study is also researching the relationship between the clinical and genetic characteristics of Rett syndrome and is an international leader in this area.

November 2005 - National snapshot of children's development

The Australian Early Development Index (AEDI), an initiative of the Centre for Community Child Health (CCCH) (a key research centre of the Murdoch Childrens Research Institute) in partnership with the Telethon Institute for Child Health Research (TICHR), surveyed over 16,700 children in 25 communities across Australia.

The AEDI is a powerful tool for creating communities where all children can thrive and grow to fulfil their potential. It assists communities to understand how their children are doing in crucial areas of development such as physical health, language and communication, emotions, behaviour and social competence. Communities can use their results to put effort and resources into services and programs for young children so that all children make the best possible start as they enter primary school.

Findings of the AEDI were announced in Broadmeadows, Melbourne in November 2005, by the Minister for Family and Community Services, Senator Kay Patterson.

EDI, an initiative of the Telethon Institute and the Centre for Community Child Health in Melbourne, is funded by the Australian Government Department of Family and Community Services with corporate support from Shell in Australia.

## Intellectual Disability Exploring Answers

The IDEA (Intellectual Disability Exploring Answers) database held a symposium on Intellectual Disability and Autism in November, 2005 at the Telethon Institute for Child Health Research to present clinical and research advances around intellectual disability. Presentation topics included the clinical investigation of a child with Global Developmental Delay, the impact of childhood disability on siblings and genetics and autism. The database currently uses the Heber system to classify the causes of intellectual disability, which in almost half of the cases is unknown. Other international systems of classification were discussed.

## Consumer and Community Participation

The Institute's commitment to Consumer and Community Participation made exciting progress in 2005. Some of the highlights which took place over then year include:

The development and implementation of an Institute wide policy on consumer and community participation at the Institute and the subsequent establishment of a Joint Institute / SPH Steering Committee's which collaborates with groups such as the Health Consumers Council (WA); Cochrane Consumer Network; the Cancer Foundation (WA); the Down Syndrome Assoc.; Diabetes WA; Arthritis Foundation (WA); and Aboriginal Health, to work through the many tasks associated with implementing a consumer and community participation strategy at the Institute.

The Raine Study Consumer and Community Participation Forum held in September with participants and their families. This forum gave very valuable feedback and insights into the families' perceptions of

being involved in the Raine Study. The feedback, in particular the information from the participants themselves, will lead to the establishment of a Raine Study Youth Group in 2006. It is envisioned this group will have an opportunity to be involved at a management level in planning for future activities of the Raine Study.

The Rett Syndrome Study established a parent reference group, which has membership from all over Australia and holds meetings via a teleconference. The group has so far given feedback on the information they would like to see in their newsletter and the planning for a national conference which was held in Sydney in November.

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## Aboriginal Health Research

### Kulunga Research Network

Hayward C

Kulunga Research Network has undergone a period of renewal in 2005, and is now operating at full staff capacity. A steering committee comprising community and research experts has been established and met regularly in 2005. A major highlight of the year involved situating the WAACHS Communication Strategy into Kulunga Research Network, and this has provided a more strategic and focused communication and dissemination plan.

2005 saw the first full year of operation of the NHMRC-funded Indigenous Capacity Building Grant (ICBG). We have established a board of management, held 2 team workshops to assist in the planning and identification of study proposals and supervisors & mentors, professional development writing workshops, and had other opportunities for networking and to act as advocates for Indigenous health. Also of note was the successful identification and recruitment, in late 2005, of a suitable coordinator for the ICBG to aid in maximising the benefits of the grant for all involved.

Kulunga Research Network secured an important consultancy tender from the Department of Health to undertake a mental health scoping study with Indigenous communities. The Project Planning Group developed a draft Model of Service Delivery which became part of the consultancy to design and implement a process to consult with a cross section of key stakeholders to seek their feedback on the model design and support for this approach requesting that the Network provide a final report to the Planning Group by January 2006.

### Kulunga Communication Strategy

Edwards TL, Butler K

Ensuring appropriate engagement with Indigenous communities is considered one of the many challenges of conducting Aboriginal health research. To ensure Indigenous engagement in Kulunga's research, a communication strategy has been developed. This strategy also includes appropriate dissemination methods for reporting research

outcomes back to the Aboriginal community.

### Footprints in Time – the Longitudinal Study of Indigenous Children (LSIC)

Silburn S, Zubrick S, Hayward C, Seymour E, Param R, Brown N, Williams A, Mitrou F, Freemantle J, Faulkner S, Lee S

This study aims to improve the understanding of, and policy response to, the diverse circumstances faced by Aboriginal and Torres Strait Islander children, their families, and communities. Footprints in Time aims to provide a data resource that can be drawn on by Australian governments, researchers, service providers, parents and communities. It is anticipated this resource will provide a better insight into how a child's early years affect the way they develop and mature.

In 2005 the Institute conducted a trial of the methodology and tools proposed for use in the LSIC study. Two trial sites of the Torres Strait Islands/Cape York and the Australian Capital Territory/Queanbeyan were selected. Institute involvement included developing research materials such as consent forms, conducting fieldwork training of research staff and undertaking fieldwork interviews and focus groups in the Torres Strait Islands and Cape York.

### Rio Tinto Child Health Partnership

Wilkes T, Hayward C, Param R, Edwards TL, Faulkner S, Kepert M, Lee S

The Rio Tinto Child Health Partnership aims to deliver improvements in Aboriginal and Torres Strait Islander child and maternal health across Western Australia, Queensland and the Northern Territory.

There are three key projects:

1. Modelling the Western Australian Aboriginal Child Health Survey in the Northern Territory and Queensland;
2. National fetal alcohol syndrome prevention strategy; and
3. Development of workforce strategies for Indigenous community health workers.

While different states are leading different projects, all three States maintain regular communication to align, support and inform local community level implementation. In 2005, notable achievements include the successful modelling of the WAACHS data for Qld and NT, in addition to agreement by the Australian Health Ministers Advisory Council (AHMAC) to consider modelling the WAACHS in other States.

#### State-wide Aboriginal Mental Health Support Service Consultancy

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Pearson G, Bedford S, Hayward C

The WA State Health Department under its Western Australian Mental Health Strategy (2004 - 2007) and specifically through Key Initiative Three of this Strategy - Community Mental Health Services- committed to the development of a state-wide Aboriginal Mental Health Community based Service that would increase the Department's capacity to provide culturally secure mental health services to Aboriginal people in the State.

A three stage consultancy process resulted in 70 completed survey questionnaires being returned from a broad cross section of stakeholders as well as 42 group and/or individual consultation sessions (involving over 110 people) across Western Australia providing feedback on the proposed Model.

A report based on these findings with recommendations have been presented and endorsed by the Project Planning Group.

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

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Lehmann D, Tennant M, Silva D, Jacoby P, Johnston J, Smith S<sup>1</sup>, H Wright<sup>2</sup>, E Kite<sup>3</sup>, G Merritt<sup>3</sup> Kulunga Research Network (ICHR), Coates H<sup>4</sup>, Lannigan F<sup>4</sup>, Weeks S<sup>5</sup>

<sup>1</sup>Telethon Institute for Child Health Research, <sup>2</sup>Port Hedland Regional Hospital, <sup>3</sup>Combined Universities Centre for Rural Health, <sup>4</sup>Princess Margaret Hospital, <sup>5</sup>Professional Hearing Services

Swimming pools were built in four remote Aboriginal communities in Western Australia in

2000. A "before and after" study of children in two of these communities showed a reduction in burden of skin infections and otitis media.

In the last year we have been concentrating our research on documenting morbidity of children living in Jigalong and Mugarinya to see if there has been any change in clinic attendance and antibiotic treatment since the pools were opened.

This required another visit to each community to obtain information from the children's medical records. Initial analysis suggests that antibiotic prescription rates in one community have fallen since the pool was opened and that attendance at the clinic for skin disease in both communities has declined. The results are currently being prepared for publication.

A presentation at the Fifth Extraordinary International Symposium on Recent Advances in Otitis Media held in Amsterdam, The Netherlands, was well received.

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

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Nichols F, Stokes A, Johnston J, Monck R, Jeffries-Stokes C, Lehmann D in collaboration with Nguntju Tjitji Pirmi Inc and Bega Garnbirringu Health Services Aboriginal Corporation.

This largely qualitative project, a sub-set of ICHR's Kalgoorlie Otitis Media Research Project, investigated maternal smoking and breastfeeding patterns and characteristics; and Aboriginal perceptions of related social determinants and appropriate interventions. Results were drawn from both cohort (280 Aboriginal and non-Aboriginal mothers) and qualitative study (55 Aboriginal participants) databases.

Results indicated that, in line with national figures, smoking was common among both Aboriginal and non-Aboriginal mothers—with higher rates in the Aboriginal population. Infant feeding patterns indicated that exclusive breastfeeding among Aboriginal mothers was below national and international targets. Maternal smoking and infant feeding characteristics indicated that different factors may influence the decisions of Aboriginal and non-Aboriginal mothers regarding these

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behaviours.

Study findings pointed consistently to stress (and by way of stress-response, to freedom-seeking behaviour) as a pervasive component in the lives of many Aboriginal people and as a central social determinant 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. Some of these activities are already underway.

Findings were presented at the 2005 International Breastfeeding Conference in Hobart, at the 36th Public Health Association of Australia Annual Conference in Perth and the Goldfields Ear Health Conference in Kalgoorlie.

## Western Australian Aboriginal Child Health Survey (WAACHS)

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Blair E, Butler K, Cox A, D'Antoine H, Dalby R, De Maio JA, Griffin J, Hayward C, Johnston J, Lawrence D, Li J, Milroy H, Mitrou FG, Param R, Pearson G, Pilkington B, Scott L, Seymour E, Silburn SR, Wilkes E, Zubrick S R

The WAAHCS is an extensive State-wide survey of Indigenous children aged 0-17 years undertaken by the 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 Research 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. 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.

In 2005, Volume 2 of the results was released detailing the social and emotional well being of Aboriginal children. Worthy of note, are a few of the many findings in the Volume:

There were an estimated 22,900 Aboriginal children aged 4 to 17 years living in WA at the time of the Survey. Of these children, 24% were assessed from questionnaires completed by their carers as being at high risk of clinically significant emotional or behavioural difficulties. This compares with 15% of children in the non-Aboriginal population. An estimated 26% of Aboriginal children aged 4 to 11 years were at high risk of clinically significant emotional or behavioural difficulties, compared with 17% of children in the non-Aboriginal population from the same age group.

A variety of social circumstances, health conditions and lifestyles experienced by individual children, their carers and families were associated with emotional or behavioural difficulties in Aboriginal children. There are clear associations between family and household factors and risk of clinically significant emotional or behavioural difficulties experienced by Aboriginal children and young people. The factor most strongly associated with high risk of clinically significant emotional or behavioural difficulties in children was the number of major life stress events (e.g. illness, family break-up, arrests or financial difficulties) experienced by the family in the 12 months prior to the survey. Of children aged 4 to 11 years, 42% were at high risk of clinically significant emotional or behavioural difficulties in families that had experienced 7 or more life stress events compared with 25% of children in families experiencing 3 to 6 life stress events and 15% in families experiencing 0 to 2 life stress events. Similarly for children aged 12 to 17 years, 34% were at high risk of clinically significant emotional or behavioural difficulties in families that had experienced 7 or more life stress events compared with 19% of children in families experiencing 3 to 6 life stress events and 12% in families experiencing 0 to 2 life stress events

## WAACHS Communication Strategy

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The findings reported in this volume highlight the magnitude and urgency of the emotional and

behavioural difficulties faced by many Aboriginal communities and families. Importantly, they also include information on those children and young people who are doing well and living healthy and resilient lives – despite past or current adversity. Understanding how they have achieved these positive outcomes and finding adaptive ways of coping with hard and changing times will guide the development of policies and programs to help more individuals and families to have better outcomes. The Survey provides the first scientific evidence of the long-term effects on the health and wellbeing of children of having a carer who was forcibly separated from their natural family by a mission, the government or welfare.

In addition to numerous scientific meetings in which these data have been reported throughout 2005, there have been several State and federal policy meetings in which the findings have been presented and discussed to encourage uptake and application. A substantial effort is also underway through the Kulunga Research Network in the communication and dissemination of the findings with over 60 regional seminars and presentations completed during this year.

Currently the WAACHS team is preparing to release the findings for Volume 3 – Improving the Educational Experiences of Aboriginal Children and Young People in March 2006. The research team is also supporting the work of “Footprints in Time” – the National Longitudinal Study of Indigenous Children.

#### Nutrition in the Western Australian Aboriginal Child Health Survey (WAACHS)

Oddy W, Kickett-Tucker C, de Maio J, Lawrence D, deKlerk N, Lehmann D, Cox A, Stanley FJ, Silburn SR, Zubrick SR

The objective of this study was to examine early infant feeding effects on recurrent infections in Aboriginal infants and children.

Families in Western Australia of Aboriginal or Torres Strait Islander descent were in scope for participation in the Survey. A stratified multi-stage sample used an area-based frame compiled from the 1996 Australian census. A total of 1,999 families

provided data from 5,289 children aged 0-17 years (age-groups 0-3, 4-11, 12-17).

Data were collected on area of residence, early infant feeding and recurring chest, ear and gastrointestinal infections as well as infant gender, birth-weight, smoking in pregnancy, maternal/carer education, level of socioeconomic disadvantage, and level of relative isolation.

Breastfeeding for 3 months or longer and being in the top 50% of socioeconomic disadvantage were significant protective factors against chest infections. Rates of infections continue to be unacceptably high in indigenous infants and children. Interventions to increase breastfeeding and to reduce the prevalence of low birth-weight should be primary health goals in indigenous communities for the benefits of Aboriginal infants and children.

## Epidemiology of Infectious Disease

### Pathways to hospitalisation with infection

Lehmann D, Moore H, Carville K, Jacoby P, de Klerk N in collaboration with Burgner D, Richmond P (School of Paediatrics and Child Health, University of Western Australia), Hall G (National Centre for Epidemiology and Population Health, Canberra)

This study utilises the population-based WA Data Linkage System to investigate the principal reasons young WA children are admitted to hospital and to increase our knowledge about infectious disease morbidity.

Our cohort consisted of all WA births between 1st January 1990 and 31st December 2000 and their associated hospital admissions before age 2 years. In this cohort infections were the predominant reason children were admitted to hospital, with the admission rate for infections being 4.6 times higher in Aboriginal than in non-Aboriginal children.

Upper respiratory tract infections (including otitis media), lower respiratory tract infections and gastrointestinal infections were the main causes of admission for infection. Admission rates changed significantly over time with admissions due to infection increasing in non-Aboriginal children from 1992 to 2000 but decreasing in Aboriginal children over the same time. These diverging temporal trends

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led us to investigate specific infections further including acute lower respiratory infections and meningitis.

Acute lower respiratory infections account for one fifth of all admissions due to infection. Bronchiolitis admissions have significantly increased in both non-Aboriginal children and Aboriginal children under age 2 years, while pneumonia admissions have increased in non-Aboriginal but declined in Aboriginal children. A diagnostic shift from asthma and bronchitis to bronchiolitis is evident in children in their second year of life. Meningitis admissions declined significantly between 1992 and 2000, following the introduction of Haemophilus influenzae type b (Hib) conjugate vaccine into routine immunisation schedules.

This study highlights the success of Hib vaccine implementation and the use of the WA Data Linkage System for surveillance of vaccine-preventable diseases. We have investigated the association between some pregnancy complications and subsequent hospitalisation of young children with infections. The results 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. This now requires further investigation.

## Twins, siblings and infectious disease

Burgner D, Donohue K, de Klerk N, Richmond P, Hansen J, Firth M, Colvin L

Infectious disease is ever-present in childhood and infection is the most common hospital admission diagnosis for children but the determinants of infection severity are unknown.

During 2005 the group continued investigating the genetic susceptibility to childhood infection and inflammation using data from the WA Twin Register and the Maternal and Child Health Research Database. The next phase of the research will expand to include investigations of sibling effects and infectious disease susceptibility. Good population-based, de-identified data exists in Western Australia for grouping hospital admissions firstly for each child, and then for groups of children with the same mother. Hospital admissions for

infections such as asthma and procedures such as adenotonsillectomy and grommet insertion will be examined and a sibling risk ratio determined for the more common diagnoses for hospital admission within the infectious disease category.

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

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

Otitis Media (OM, middle ear infection) can seriously affect childhood development, school performance and subsequent social and economic well-being.

In order to develop appropriate interventions, Aboriginal and non-Aboriginal newborn babies in the Kalgoorlie-Boulder area were followed regularly until the age of two years to investigate the 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 with all data entry and cleaning completed by April 2005. Lehmann D, Stokes A, Coates H, Cripps A and Weeks S gave presentations at the Fifth Extraordinary International Symposium on Recent Advances in Otitis Media held in Amsterdam, The Netherlands.

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 ear drum at least once. Hearing loss was detected in 65% of Aboriginal and 23% of non-Aboriginal children at age 12-17 months.

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.

A total of 436 saliva samples (for immunological investigation) and 509 nasopharyngeal specimens (to detect viruses and bacteria 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 49%, 41% and 50% in Aboriginal children; for comparison, carriage rates in non-Aboriginal were 25%, 11% and 25%, respectively. Thirty-seven percent of Aboriginal and 11% of non-Aboriginal babies are colonised with the pneumococcus before the age of two months. *Staphylococcus aureus* carriage was highest under age 1 month (55% Aboriginal and 61% non-Aboriginal) and always higher in non-Aboriginal than Aboriginal children. Non-Aboriginal children had higher carriage rates of *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* in winter than in summer but season had a minimal effect on carriage rates in Aboriginal children. This information has recently been submitted for publication.

A total of 406 samples were tested for adenovirus, rhinovirus, respiratory syncytial virus (RSV), coronavirus, influenza viruses A and B, parainfluenza virus and human metapneumovirus, and a further 625 samples were tested for a subset of 4 of the original seven viruses. Adenovirus and rhinovirus are the most common viral agents found in the nasopharynx. Overall identification rates for rhinovirus were 24% in Aboriginal and 16% in non-Aboriginal children; equivalent figures for adenovirus carriage were 8% and 3%, respectively.

Current bacteriological and viral investigations are focussed on the interactions between pathogens in the nasopharynx, with preliminary investigations indicating that rhinovirus infection predisposes children to simultaneous infection with bacterial OM pathogens.

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

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Lehmann D<sup>1</sup>, Moore H<sup>1</sup>, Harrison C<sup>1</sup>, Rooney K<sup>1</sup>, Bayley K<sup>2</sup>, Brown L<sup>2</sup>, Murphy D<sup>3</sup>, Keil T<sup>2</sup>, Richmond P<sup>4</sup>, C Giele<sup>5</sup>, Dowse G<sup>5</sup> for the VISN Network.

<sup>1</sup>Telethon Institute for Child Health Research, <sup>2</sup>Department of Microbiology, Princess Margaret Hospital for Children, <sup>3</sup>Public Health Laboratory, Queensland, <sup>4</sup>School of Paediatrics and Child Health, University of Western Australia, <sup>5</sup>WA Department of Health

The Vaccine Impact Surveillance Network (VISN) was established in 1996 to collect and analyse information on vaccine-preventable diseases and evaluate the impact of vaccines and vaccination programs on these diseases.

Invasive Pneumococcal Disease (IPD) is the disease caused by *Streptococcus pneumoniae* invading a normally sterile site such as blood and cerebrospinal fluid. IPD is a major cause of pneumonia, septicaemia, bacteraemia and meningitis worldwide.

Although IPD only became a notifiable disease in Australia in 2001, VISN has collected epidemiological and microbiological data on all reported cases of IPD since 1996 through review of hospital records and reporting from Public Health and Infection Control Units. Data collected include the clinical diagnosis, management, risk factors, vaccination history, outcome, pneumococcal serotype and antibiotic resistance.

A 23-valent pneumococcal polysaccharide vaccine (Pneumovax) has been recommended since 1986 for Aboriginal adults aged 50 years or more, for younger Aboriginal adults with known risk factors and non-Indigenous Australians aged 65 years or more, and since 2005 has been fully funded by the Federal Government. In 2001, the 7-valent conjugate pneumococcal vaccine (Prevenar) was licensed for

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use in Aboriginal and Torres Strait Islander children and other children with known risk factors. Since January 2005 all Australian children are offered Prevenar.

Much of 2005 was spent collating and completing collection of essential data for all records of IPD from clinical and laboratory databases for the period 1996 to 2000, and then merging with current databases from 2001 to present.

In December 2005 there were a total of 1655 episodes of IPD on the VISN databases over the 10 year period. In 2005 there were 138 reported cases of IPD and 21 deaths compared with 195 cases and 21 deaths in 2004. The number of cases in children aged less than 5 years fell from 49 in 2004 to 21 in 2005. Ongoing surveillance for IPD is essential to monitor the impact of pneumococcal vaccines. In April 2006, we will present these 10 years of epidemiological data on IPD at the 5th International Symposium on Pneumococci and Pneumococcal Diseases in Alice Springs.

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

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Lehmann D<sup>1</sup>, Reeder J<sup>2</sup>, Holt P<sup>1</sup>, Pomat WS<sup>2,3</sup>, Richmond P<sup>3</sup>, Phuanukoonnon S<sup>2</sup>, van den Biggelaar A<sup>1</sup>

<sup>1</sup>Telethon Institute for Child Health Research, <sup>2</sup>Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea, <sup>3</sup>School of Paediatrics and Child Health, University of Western Australia

Throughout the world an estimated one million children die annually from pneumococcal disease, the majority in early infancy. This study is designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in 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. Recruitment into the study began in May 2005 and sixty babies were enrolled by the end of 2005.

In an extension of this project, D Lehmann began supervision of a post-doctoral research fellow (IA Laing), who will be investigating the contribution of human genetic susceptibility to nasal bacterial carriage, development of immune/vaccine responses and the incidence of pneumonia in this population. Funding for the genetics studies includes the Community Health and Tuberculosis Australia (CHATA) Ann Woolcock Australian Research Fellowship and a grant from the University of Western Australia Research Grants Scheme 2006.

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

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Lehmann D, de Klerk N, Firth M (ICHR) in collaboration with Vail J (Kyogle, NSW) and Alpers MP (Centre for International Health, Curtin University of Technology)

Following a report of increased risk of death associated with diphtheria-tetanus-pertussis (DTP) and oral polio vaccination of children living in rural areas of Guinea-Bissau, the World Health Organization Department of Vaccines and Biologicals sought proposals to determine the effects of routine infant immunisation on survival in

areas of high mortality.

We investigated the impact of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. Continuous monthly demographic surveillance enabled us to identify births, deaths, migrations, and immunisation status of all children born in Tari between 1989 and 1994.

The study determined the effect of DTP, BCG and measles vaccinations on mortality in the first two years of life and found no deleterious effects of infant immunisations. Our findings have been published in an international journal. There has also been an investigation into some statistical methodology issues concerning longitudinal and observational data sets such as this one. A paper has almost been finalised that compares the potential impact of the varying assumptions that different studies have made around the world.

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

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Lehmann D, de Klerk N, Firth M in collaboration with Whiting D, Dyke J, Dyke T, Wilson J, Rogers S, Gehala D, Tumbiako E (formerly Papua New Guinea Institute of Medical Research), Alpers M (Centre for International Health, Curtin University of Technology)

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

## Developmental Epidemiology

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

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Kurinczuk J (University of Oxford, UK), Zubrick S, Silburn S, Parsons D, Moore K, Dragovic S, Burton P (University of Leicester, UK), Dixon G, in collaboration with VP Dawes (formerly Health Department of Western Australia), Plant A (Curtin University).

The RASCALS Study (formerly known as the 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 continued 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 immunization, 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.

The RASCALS Study completed collecting information from the 1995 birth cohort during the first quarter of 2004. The data collection from the 1996 cohort was completed during the first half of 2005 and was enhanced following parental consent, with information obtained from the study children's teachers which was finalised by 30 June 2005. The RASCALS study remains one of the few key longitudinal studies in Australia and it is expected the data will provide invaluable information for future researchers over the next several years to inform on key issues of disease prevention and health promotion.

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## Looking at Language - Twins and Singletons with Specific Language Impairment

Rice M, Institute for Lifespan Studies, University of Kansas, Zubrick S, Taylor K, 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 twins and single-born children and their families.

The LOOKING at Language study aims to understand more about the relative effects of genetic factors, and shared and non-shared environmental effects, on language acquisition and risk of SLI in singletons and twins at ages 2, 4 and 6 years. In the fourth year of the project, progress is significant. We have consent for direct assessment for 702 twin pairs (1404 children) and 237 singletons. In addition, we recruited and assessed 404 family members of children at risk for language acquisition, for a total of 2,045 persons. The obtained data subdivides into two general types: 1) Direct behavioral assessments of language and cognition, and 2) Questionnaire data of child, maternal, and family variables. The protocols for language and cognitive assessment are age-adjusted to match the child-to-adult range for families as well as the target twins and singletons.

## The WA Twin Child Health (WATCH) Study.

Hansen J, Alessandri P, de Klerk N, Croft M, James A

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

Hansen J, Alessandri P, de Klerk N, Croft M, James A

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 seven 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 analysing the large amount of data that has been collected.

Results from this study have shown that exhaled nitric oxide (eNO) was influenced by age, sex, body mass index (BMI) and smoking status. There was a strong relationship between eNO and doctor-diagnosed asthma, increased serum IgE levels,

increased airway responsiveness and increased blood eosinophils. In addition, it was shown these relationships were strongly modified by an individual's atopic status, with a positive relationship being shown in atopic individuals, whereas non-atopic individuals showed no relationship. Exhaled nitric oxide was shown to have a significant genetic contribution, with heritability estimates in this population ranging from 34-80%.

To our knowledge, this is the first study to show that eNO has a separate genetic pathway as well as sharing some genetic pathways with IgE and airway responsiveness. Future directions for this study will include the genotyping of all study participants using stored DNA.

#### The Raine Study - Physical activity levels in early adolescence, antecedents and consequences

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, an ongoing supporter of the project. This Study represents a multi-faceted collection of 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.

More than 1600 teenagers aged 13 years, participated in our most recent follow-up, which focused on physical activity levels in early adolescence. We were able to obtain important information in relation to physical activity levels, physical fitness, motor competence, nutrition, posture, joint mobility, back muscle strength, blood pressure, respiratory function, allergy, and stress responsiveness.

In addition, the 13 year follow-up involved the collection of information regarding child mental health and family functioning, general health, and school achievement. Blood was also 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 at the University of Western Australia, and the Schools 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, menstrual disorders, musculo-skeletal development, asthma and allergy, and stress responsiveness.

In addition, consumer and community participation became an important new focus to the Raine Study in 2005. A workshop was held with Raine Study children, parents and carers to discuss ways in which consumer and community participation can be increased in relation to the management of the Study. Children participating in the Study will now be encouraged to become involved with the Raine Study Youth Group which provides a forum for them to have an input into how the Study is being run.

## Birth Defects

### Folate and the prevention of neural tube defects

Bower C, Miller M, Payne J, Serna P, Oddy W, de Klerk N, Hickling S, Ambrosini G, Flicker L, Geelhoed E, Milne E

Based on data from a case control study, we investigated awareness and consumption of folate fortified foods by women of child bearing age in Western Australia. Before or during their recent pregnancy, 42% of women had noticed labels on foods that mention folate and 33% usually or always read the labels on food packaging.

Overall 53% of women were aware of foods that have folate added to them and the most frequently

consumed folate-fortified foods were cereals (69%), breads (34%) and milk (15%). Almost 80% of women consumed foods voluntarily fortified with folate and this suggests that mandatory fortification, should it be introduced, may reach most women, providing improved opportunity for prevention of neural tube defects in Australia.

We also completed a contract for Food Standards Australia and New Zealand to (1) model and assess the effect of incremental increases in folic acid intake on the incidence of neural tube defects in Australia and New Zealand; review the literature on folate (2) and prevention of cancer, cardiovascular disease and cognitive decline; and (3) folate and a possible increase in risk of cancer. These data are contributing to the consideration of mandatory fortification of food in Australia and New Zealand for the primary prevention of neural tube defects.

## Folate intake and the primary prevention of non-neural birth defects

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Bower C, Miller M, Payne J, Serna P

In this study, we investigated, using a case control study, whether maternal intake of folate in the periconceptional period protected against infants having orofacial clefts; congenital heart defects, urinary tract defects, limb reduction defects or other major birth defects. Neither folic acid supplements nor dietary folate intake in women not using supplements were significantly associated with a reduction in risk in any of the case groups.

In contrast to neural tube defects, WA population data for orofacial clefts, heart defects, limb reduction defects and urinary tract defects showed no fall in prevalence since the introduction of folate promotion and voluntary food fortification. This study provides no evidence of folate being an important factor in the prevention of birth defects other than neural tube defects.

## Fetal Alcohol Syndrome in Australia

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Bower C, Elliott E, Haan E, Payne J, D'Antoine H, O'Leary C, Colvin L, Kulunga Research Network

FAS is caused by maternal alcohol consumption during pregnancy and represents the most severe

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; and evidence of damage or dysfunction of the central nervous system.

Data from the Western Australian Birth Defects Registry suggest a birth prevalence for FAS of 0.18 per 1,000 live births (0.02 per 1,000 non-Indigenous live births; 2.76 per 1,000 Indigenous live births).<sup>1</sup>

We have conducted national surveillance of FAS with the Australian Paediatric Surveillance Unit (APSU) over the past four years. There were 76 reported cases that met the definition for FAS (suspected FAS or partial FAS) used in this study.<sup>2</sup> The median age at the time of diagnosis was 2.8 years (newborn to 12 years), 51% were male, and 61% were identified as Indigenous. Only 42% of these children were living with their biological parent(s), 17% lived with grandparents or other relatives, and 40% were adopted or fostered. 76% were exposed to other substances in utero including nicotine (65%) and marijuana (25%). All children had been referred to one or more health related agencies including specialty paediatric services (78%), child development services (49%), department of community services (67%) and remedial education services (30%). The APSU study of FAS has provided valuable descriptive data and an estimate of the number of children under 15 years of age with newly diagnosed FAS between 2001-2004. The APSU data show that FAS contributes to significant social, medical and educational burdens to affected children, families and the community.

We have also determined health professionals' knowledge, attitudes and practice in relation to FAS and alcohol consumption in pregnancy. Results from the Survey of Health Professionals in Western Australia<sup>3</sup> show that of 1,143 health professionals, 12% identified the four essential diagnostic features of FAS. Only 2% felt very prepared to deal with FAS and most wanted information for themselves and for their clients. Of the 656 health professionals who cared for pregnant women, 45% routinely ask about alcohol use in pregnancy, and 25% provide information about the consequences of alcohol consumption in pregnancy and 13% provide advice

that is consistent with the NHMRC guideline on alcohol consumption in pregnancy.

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#### Cerebral palsy and birth defects

Blair E, Al Asedy F, Badawi N, Bower C

Data from the 1980-1994 Western Australian birth cohorts (355,659 neonatal survivors) were linked to the Cerebral Palsy Register (941 links) and the Birth Defects Registry (17,070 links). Associations between cerebral palsy and birth defects were found.

The origin of the increase in odds of an association between non-cerebral defects and acquired cerebral palsy arose primarily on account of cardiac defects. For congenital cerebral palsy the association with non-cerebral birth defects arose partly from ascertainment bias and partly from defects known to be associated with cerebral defects (but not identified in these data). However, a significant portion remained unexplained.

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

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

Analyses of hospital discharge data from our study of health outcomes in children born after assisted

reproductive technologies (ART) are continuing. Record linkage of midwives' data to the WA Birth Defects Registry is now complete and analyses of birth defects in children born after ART (1993-2002) compared with the remainder of infants born in WA over the same time period will be carried out this year.

We have carried out a systematic review and meta-analysis of all the published literature examining birth defects in children born following ART compared with naturally conceived children. Our results indicate a statistically significant 30-40% increased risk of birth defects in assisted conception infants. Our paper describing this work was published in *Human Reproduction* in 2005 generating national media interest. The results have implications for the counseling of couples seeking ART treatment.

We have also carried out a comparison of birth defect data reported by three WA IVF clinics to the Australian National IVF Register with birth defect data identified by record linkage of all children conceived at these clinics between 1993 and 1997 to the WA Birth Defects Registry. We are currently preparing the results of this comparison for publication in collaboration with the clinics involved.

Three investigators (Kurinczuk, Hansen and Bower) were asked to contribute a chapter titled "Methodological considerations when designing studies to examine the health of children born following ART" to a book titled "Health and Welfare of ART Children" (Editor, Sutcliffe AG). The book is currently in press and should be published mid-year.

The Chief Investigator (Hansen) was invited to participate in a workshop organised by the National Institutes of Health in Washington DC in September 2005. The aims of this workshop were to review current research, identify gaps and develop a research agenda to better define the range of adverse health outcomes associated with infertility treatments and try to understand the mechanisms underlying these outcomes. The CI was asked in particular to present a talk on 'international data sources for assessing health outcomes in ART children'. The data presented highlight the importance of the WA Reproductive Technology Register which is one of only four registers worldwide that can be linked to other population-based

health registers to obtain information about longer-term health outcomes in ART children.

Future work on this project will involve linkage to cerebral palsy and intellectual disability data.

## Co-occurrence of Birth Defects and Intellectual Disability

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

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 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), other chromosomal 64.2% (67.9). Birth defects were categorized according to system in the 96.8% of children with non-chromosomal anomalies and the corresponding % with ID were nervous 38.6; spina bifida 10.8; cardiac 4.2; gastro-intestinal 2.2; urogenital 2.6; musculo-skeletal 3.6; other non-chromosomal 7.0; and multiple systems 12.3.

Birth defects were found in 30.2% of children with an ID compared to 4.6% of children with no ID, giving a PR of 6.5. Children with birth defects comprised 27.7% of the group with mild or moderate ID and 54% in those with severe ID. Non-chromosomal defects were found in 20.6% of those with any ID (PR=4.5). Prevalence ratios not related to the nervous system ranged from 1.7 for gastrointestinal defects to 10.8 for those with multiple defects. Adjusting for sex, mother's age, race, parity, plurality, birth weight and gestational

age had little effect on the prevalence ratios.

The data are useful for those providing services for children with developmental disabilities especially for predicting family support and respite and accommodation requirements for children and adults with severe intellectual disability.

## National - Rett syndrome: determinants of outcome and burden

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Leonard H; Bower C; deKlerk N; Silburn S; Christodoulou J; Ellaway C; Fyfe S; Hall S; Msall M; Dr Nagarajan L; Reilly S; Woodhead H.

As the Australian Rett Syndrome study 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 every two years on their child's functional ability in daily living, behaviour, hand function, medical conditions, and use of health and education services and every four years on family health and functioning. The questionnaire administered in 2004 also sought information on health and other costs and on resource utilisation. During 2005 collection of the 2004 questionnaires was finalised and data entry undertaken. Questionnaires were completed by mail or over the Internet and some telephone interviews were conducted for families unfamiliar with English or with literacy problems.

Genetic and clinical data are also collected as part of the project. The latter include clinical assessments, EEGs, ECGs, and bone densitometry. EEGs were more easily available for younger subjects and during 2005 with the cooperation of the network of child neurologists around Australia EEG data have now been collected on 52 of the study participants. During 2005 the infrastructure for the undertaking of bone densitometry assessments was set up in New South Wales, Victoria and Queensland. By the end of the year bone density assessments were well

underway at the Children's Hospital, Westmead and the process will continue at the other centres in 2006.

Another important and innovative source of data for this study is video footage provided by the subjects' families. During 2005 a video scoring system was developed to assist with the coding of the video material which had been collected mostly during 2004. This involved a multi-disciplinary approach which included input from psychologists, physiotherapists and speech therapists. Coding in the various domains eg oromotor function and mobility commenced.

During 2005 national collaborations for instance with the Children's Hospital at Westmead, Sydney and the Royal Children's Hospital, Melbourne were maintained and staff visited these centres to collect clinical data. Some new international collaborations were initiated, for example with Dr Bronwen Burford from the University of Glasgow, Associate Professor Walter Kaufmann from Johns Hopkins University and Professor Alan Percy from the University of Alabama. Work continued with Dr Hayley Archer from the University of Wales and Professor Michael Msall from the University of Chicago.

In 2005 we officially set up our Consumer Reference Group which involves regular teleconferences with families across Australia. This was led by Orla McIlroy with input from Anne McKenzie. Particular highlights of the year were the two workshops, one for parents and one for clinicians held at the Kerry Packer Institute, at the Children's Hospital at Westmead, Sydney and sponsored by the Australian Paediatric Surveillance Unit.

Analytical investigations using data relating to different aspects of the study continue to be undertaken and publications prepared and during 2005 ten articles relating to the study were either published or in press.

The work undertaken covered a range of topics from the general epidemiology (ie how common is Rett syndrome) to complex aspects of the genetics. We were able to provide estimates of life expectancy to the age of 25 years in Rett syndrome and indications that life expectancy may

be influenced by the specific genetic mutation with which the person is affected. We were able to describe the behavioural characteristics of Rett syndrome and some of the variability in these and to relate aspects of early development to the likelihood of later onset of scoliosis. We also investigated which factors might be most likely to be associated with early onset of seizures.

In relation to the burden of this condition on the family we also investigated the factors associated with physical and mental health in the mother of the child with Rett syndrome. In conjunction with Professor David Ravine at the Western Australian Institute for Medical Research we identified a rare exon 1 MECP2 mutation in one of our cohort and were able to describe the clinical characteristics in this case.

Two other important outcomes in 2005 related to our demonstration of the ability to diagnose Rett syndrome from a baby tooth in a child who had died 14 years previously and the role of MECP2 (the Rett syndrome genetic mutation) in newborn encephalopathy in males (that is in some baby boys who develop neurological problems very early in life).

#### InterRett

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Leonard H, Anderson A, De Klerk N, Fyfe S, Ravine D

During 2005 the AussieRett group continued to manage the international phenotype database InterRett.

Funded by the International Rett Syndrome Association, InterRett collects data from families and clinicians around the world through online and paper based questionnaires.

In 2005 the family questionnaire was translated into Spanish, Italian, German and French to assist non-English speaking families to participate. The online questionnaire and website has also been translated into Spanish providing an opportunity for families in Spanish speaking countries particularly in South America to participate in research efforts.

To date the database contains over 900 cases from 28 countries satisfying the prime objective

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of creating a sufficiently large sample size to allow comparison of genetic with phenotypic characteristics. It is envisaged that subsets of this valuable dataset can be used to support various research initiatives being undertaken around the world. To facilitate this, the international reference panel that guides InterRett is currently developing formal guidelines for data access.

As a freely available online resource, InterRett also provides an innovative and efficient mechanism for disseminating information on Rett syndrome research. The online output database allows users to create graphs of the de-identified data providing an overview of the variability of phenotype across and within mutation types. The submission of bulk data is extremely valuable and during 2004 Spain, Israel and Canada submitted bulk data and customised databases were provided to clinicians in France and Mexico for collection of data on multiple cases.

## Down syndrome

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

Leonard H; Bower C; deKlerk N; Silburn S; Fyfe S; Hall S; Msall M.

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, families caring for children and adults with Down syndrome, and early intervention programmes. 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 are:

- To document the current health, functioning, needs (including psychosocial, employment, and accommodation needs), and behavioural 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.

The study questionnaire developed in 2004 was particularly comprehensive because it included considerable input both from the Down Syndrome Association of WA and Disability Services Commission. Families had the option of completing the questionnaire on paper or online. Telephone interviews were also offered to those who preferred this option.

Data collection was completed during 2005 and we were fortunate in being able to achieve a response of 72% despite the challenges that were encountered in this process.

We are extremely grateful to all the Western Australian families who have participated in what we expect will be a landmark study. In conjunction with the Down Syndrome Association of Western Australia we are currently seeking financial support to release the findings from this study as a report which will be distributed both to participating families and relevant stakeholders.

Other work undertaken during 2005 included an editorial on the impact on Down syndrome of sociodemographic and technological changes which have occurred over the last few decades. This referred to those medical advances which have substantially improved life expectancy and quality of life especially for those Down syndrome infants born with congenital heart defects, the changes in attitude and access to health care for children and adults with disabilities such as Down syndrome and the effect of prenatal diagnosis on the birth prevalence of Down syndrome.

Work has also progressed on an investigation of the impact on children who have a sibling with a disability such as Down syndrome or Rett syndrome. That particular project is examining the perceived benefits and disadvantages for the non-disabled siblings and the factors influencing these.

#### First trimester screening for Down syndrome

Hadlow N, Hewitt B, Dickinson J, Jacoby P, Bower C, O'Leary P, Breheny N, Goldblatt J, Murch A, Stock R

Two record linkage studies were conducted. In the first, two years (1999-2000) of community-based first trimester screening (FTS) were audited. All women with a singleton pregnancy in a defined health region who completed FTS (ultrasound and biochemistry) were included (n= 10,436) and outcomes were obtained for 98.4%. All scans were performed or supervised by experienced sonologists and the detection rate for Down syndrome was 90.6% with a screen-positive rate of 3.9%.

In the second study, FTS data were obtained for screening between August 2001 and October 2003. The detection rate was 83% and the false positive rate was 3.7%. Furthermore, 25% of pregnancies with other birth defects occurred among those

identified at increased risk of Down syndrome and 1 in 8 pregnancies at increased risk were found to have a significant chromosomal or structural defect.

## Child Nutrition and Development

### Breastfeeding and its effect on the risk of Sudden Infant Death Syndrome

Espaignet E, Oddy WH, Firth M, DeKlerk NH.

Data analysis is complete and scientific writing is underway for this project.

### Obesity and fast food in the Growth and Development Study

Oddy WH, Byrne S, Miller M.

Data analysis is underway in a new wave of data collection. An abstract will be submitted to the International Congress of Obesity in Sydney, September 2006. A scientific paper is in draft stage.

### Maternal obesity and the risk of birth defects.

Bower C, Oddy WH, DeKlerk NH.

Data is available from the Study of Birth Defects to test the hypothesis that maternal obesity prior to pregnancy is a risk factor for birth defects. Data analysis is underway and a scientific paper is in the draft stage.

### Early child development and breastfeeding

Oddy WH, Kendall GE, Dixon G, De Klerk NH, Zubrick S.

Two papers are planned from the West Australian Pregnancy Cohort Study to test the hypothesis that a shorter duration of breastfeeding is a risk factor for developmental and mental health problems later in childhood. Data analysis is underway and a manuscript is in preparation.

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## Dietary patterns and mental health

Di Candilo KG, Oddy, S Silburn S, DeKlerk NH, Sloan N, Li J, Kendall GE.

A study on 'the effect of follow-up phone-calls on three-day food diaries in 13 year old participants of the Raine study' was presented to the 2005 Dietitians Association of Australia (DAA) conference for the theme 'embracing diversity'. Two abstracts have also been accepted for the 2006 DAA conference for the theme 'the future of dietetics'. These studies are focused on breakfast eating habits of adolescents in the Raine study. In addition, we have been making progress on an index of diet quality for use in Raine study participants. This has involved a partnership with Prof. Lise Dubois who visited the Institute early in 2005.

Breakfast is often considered the most important meal of the day and is an important factor in the nutritional well-being of young people. Previous studies suggest that breakfast skipping/inadequate breakfast consumption may lead to poor school performance. Between 3% and 20% of children skip breakfast depending on age, with lack of time, not being hungry and body weight concerns being common reasons. Our study's purpose was to explore associations between breakfast intake and mental health and body weight in 13 year-olds.

Thanks are extended to Curtin Research Grant Schemes and Telstra Research Foundation for funding this component of the Raine Study 13 year follow-up.

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

Beilin LJ, Palmer L, Oddy WH, Mori T, Kendall G, Hands B

Funding has been obtained from NHMRC to commence the 16 year follow-up of the Raine Study cohort for diet and nutrition and cardiovascular risk factors. Ethics is being obtained currently. The 16 year follow-up is due to commence in May 2006.

## The influence of maternal overweight and obesity on breastfeeding duration.

Oddy W, Li J, Landsborough L, Henderson S, Kendall E, Downie J.

Two manuscripts have been submitted to the Journal of Pediatrics.

## Feeding Issues in Developmental Disorders (Rett Syndrome)

Oddy WH, Leonard H, Di Candilo K, Anderson A, Baikie G, Thompson S, Fyfe S, de Klerk N, Reilly S.

Analyses have commenced on feeding questionnaire, BMI Z scores and gastrostomy feeding. A draft paper is in preparation.

## Fatty Acids and Depression Project

Oddy W, Kendall G, Silburn S, Zubrick S, Blair E, Miller M

Data collection within the 13-year follow-up of the Raine Study cohort is underway. Although data collection was due for completion in December 2005, it has been extended to the end of April 2006. Response rates for questionnaires on child depression, food frequency and measurement of fatty acid intake within the cohort data collection, are over 95%. Data analyses will commence on completion of the follow-up.

## The Raine Study: nutrition, obesity and mental health

Oddy W, Kendall G, Silburn S, Zubrick S, Blair E, DiCandilo K, Sloan N, Miller M, DeKlerk N

The fatty acid and depression project funded the first two years of nutrition data collection in the Raine Study cohort. Funding was received from the Telstra Foundation to continue and complete the 13 year follow-up for nutrition and mental health data. Analyses will begin once the 13 year follow-up is completed in 2006.

## The Childhood Growth and Development Study

Byrne S, Davis E, Blair E, Zubrick S, Jones T, Silburn S

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 programmes.

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.

At the end of 2005, the Growth and Development Study has 1240 children taking part. This year the new schools we visited were Ferndale, Como, East Claremont and Subiaco and our returning families came from East Wanneroo, Mount Pleasant, Dianella Heights and Lance Holt. To date, 347 initial interviews have been completed with children, as well as 247 with parents. So far, over 200 children have come back for their one-year follow-up interviews and some families are even moving on to their 18-month follow-ups. In 2006, we will continue to follow-up all our families as well as recruiting new families. 2005 has been an active year for the Childhood Growth and Development Study. Our team members have presented study results at national conferences in Melbourne and Adelaide, and internationally in New Zealand and France. The Childhood Growth and Development Study is grateful for the support of the following organisations, Healthway and the Raine Medical Foundation.

## Measuring pre- and postnatal growth

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

The aim of this study is to identify measures of appropriateness of intrauterine and post natal growth within an individual to facilitate the epidemiological study of intrauterine growth and the development of childhood overweight and obesity. Currently used measures are indirect and have several shortcomings. Some shortcomings are overcome by expressing the dimension as the proportion of the median in optimally grown children of the same growth potential. Using neonatal measures of weight, length and head circumference from total population data, we have derived and reported equations for the optimal weight, length and head circumference in terms of the following non-pathological determinants of size: gestational duration, infant gender, maternal height, parity and age, enabling the proportion to be estimated for each individual.

A part time statistics graduate (JPG) was employed for four months from April 2005, supervised by EB and DL. Starting with the assumption that any measure of adiposity that takes height into account should be independent of height, this graduate position sought expressions of height and weight that met this criterion in Midwives and Raine data and examined their performance with age. These investigations suggest that there is no simple relationship that can be identified with fractional polynomials, between weight and height that is independent of height and age in the age range 0-10 years. Considering the expression weight/height, results suggest that the optimal value for  $n$  (to gain an expression independent of height) varies continuously with age, being close to 1 in neonates and close to 3 in 10 year olds (convention uses  $n=3$  for neonates and  $n=2$  subsequently).

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## Databases and Information Technology for Population Studies

### Record linkage and the Maternal and Child Health Research Database

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Cosgrove P, Wood M, Berinson M, Nguyen H, Murigu N

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

2005 is the second year of our collaboration with the WA Data Linkage Unit (DLU). The collaboration involved the relocation of all of our record linkage work to the DLU, co-location of staff on a part-time basis to the DLU and the provision of an annual de-identified snapshot of linked health data being provided by the DLU and the WA Department of Health to the Institute.

The DLU 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. The collaboration is working well, with feedback from ICHR researchers helping the Data Linkage Unit to continue to ensure the high quality of their linkage.

The Maternal and Child Health Database has been updated with linked health records for all children born in WA between 1980 and 2003. This has been supplemented with data from the Australian Bureau of Statistics for 2001-3. Procedures have been put in place to determine and store additional information often required by researchers, such as which hospital admissions belong to a single episode of care.

Over the last two years we have also started work on developing in-house web-based computer applications for use in the area of meta-data management and knowledge management. Meta-data is 'data about data' and these systems are designed to allow data in the Maternal and Child Health Research Database to be used as efficiently as possible, giving researchers easy access to associated key information on the data and also to

a knowledge base containing contributions by other researchers using these important data resources.

### The Western Australian Twin Register

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Hansen J, Alessandri P, Coleman K, de Klerk N, Croft M, James A, Burton P

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. This study aimed to collect detailed clinical asthma phenotype data on twins born between 1990 and 1995, and their families, and to investigate and describe the familial aggregation of childhood asthma and atopy. 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.

Future directions for the WA Twin Register include recruiting adult multiples and extending the childhood component of the Register to include all WA multiples born from 1998 onwards.

### Western Australian Mortality Database

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Freemantle CJ, Read AW, DeKlerk NH, Divitini M, Woods M, Cosgrove P, Kulunga Research Network, Anderson IP (University of Melbourne), Officer K, Bukutu C, Stanley FJ.

The First Research Report: Patterns and Trends of Mortality among Western Australian Born Infants, Children and Young People 1980-2001, was tabled in Parliament in May 2005. The Report and all its

recommendations were accepted by Parliament.

A number of the recommendations are relevant to the work being undertaken by the Institute in conjunction with the Advisory Council on the Prevention of Deaths in Children and Young People and include recommendations for:

#### Systemic improvements

- That the Western Australian State Government ensures that there is a comprehensive system of reviewing all deaths of infants, children and young people within Western Australia, such that: there are effective mechanisms for reviewing all such deaths within the State; action is taken where specific patterns of mortality are identified; and effective communication and collaboration exists between the various agencies that are involved with the mortality review process.
- That the Ministerial Advisory Council for the Prevention of Deaths of Children and Young People reports annually on the trends and patterns of infant, child and youth mortality as part of the comprehensive State system for monitoring, reviewing and reporting on trends in mortality and identifying opportunities for preventative action.
- That the Department of Health gives consideration to ensuring that there is a specialised paediatric pathology capability within the integrated system of pathology services being proposed by the Department of Health in Western Australia.

#### Specialist research initiatives

- That a qualitative study, using a verbal autopsy approach, be undertaken to better identify circumstances surrounding deaths of Aboriginal and Torres Strait Islander infants and children in Western Australia.
- That consideration is given to the support of cohort or case controlled studies to further clarify the role of maternal smoking, co-sleeping and other preventable factors in order to promote better outcomes for infants and children.
- That as part of the forward work plan for the Council, based on available and expert evidence, suites of policy and research priorities are developed for consideration by appropriate Government Agencies and Research funding bodies

in the areas of: prevention of deaths of infants, children and young people; gaining improvements in wellbeing and reduction of morbidity for infants, children and young people; and evaluation of significant existing programs which seek to reduce morbidity of infants, children and young people.

Review of the deaths of Western Australian born infants, children and young people has occurred for the years 2003 and 2004, and permission has been received to review the autopsy case reports of deaths occurring in 2005. These data will be added to the WA Mortality Database and the patterns and trends of mortality analysed. Dr Kirsty Officer and Dr Celia Bukutu have joined Dr Anne Read and Dr Jane Freemantle to assist in the review, the validation and analysis of the mortality data in order that the WA Mortality Database is maintained and the data utilised to assist in the prevention of deaths in children and young people.

Review of the autopsy case reports for sudden and unexpected deaths for the years 1998-2002, show a shift away from classification of "SIDS" towards a classification of "unascertainable". The increasing trend towards a classification of 'unascertainable' in investigations of infant deaths makes trend comparisons difficult. This is especially pertinent for the Aboriginal population as our data have shown that infants of Aboriginal mothers are more likely than those of non-Aboriginal mothers to have the cause of death classified as "unascertainable". This has implications for the accurate translation for data into policy and practice and highlights the importance of continuing to review and to validate the case of death identified in the population databases.

#### WA Family Connections Project

Glasson E, Nielsen L, Johnston M, de Klerk N

The WA Family Connections Project is a newly developed resource to support familial and genetic health research. The aim of the project is to create and store electronic links between genealogically related individuals using information from birth, death and marriage registrations as well as other data sources.

The project is coordinated through the WA Data

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Linkage Unit and the linkages are made using the same protocols and procedures that were developed for the WA Data Linkage System, which are regarded as best practice.

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 registrations that are currently held as paper records. Phase 3 will incorporate a public appeal to improve the completeness of the Family Connections database.

This new genealogical resource, the existing Western Australian Data Linkage System, and planned genetic projects place Western Australia in a strong position to undertake human genome epidemiological research to characterise genetic, environmental and gene-environment interactions at the population level.

## ARC Linkage Grant

Stanley, F<sup>1</sup>., de Klerk, N<sup>1</sup>., Bower, C<sup>1</sup>., Li, J<sup>1</sup>., Ferrante, A<sup>2</sup>., Leonard, H<sup>1</sup>., Kendall, G<sup>1</sup>., Cook, J<sup>3</sup>., Smith, M<sup>4</sup>., Mathews, R<sup>5</sup>., Krazlan, K<sup>6</sup>., Vicary, D<sup>5</sup>., Patterson, Y<sup>5</sup>., Chalmers, R<sup>7</sup>., Freemantle, J<sup>1</sup>.

<sup>1</sup>Telethon Institute for Child Health Research, UWA; <sup>2</sup>Crime Research Centre, UWA; <sup>3</sup>Department of Education and Training; <sup>4</sup>Department of Health Western Australia; <sup>5</sup>Department for Community Development; <sup>6</sup>Department of Justice; <sup>7</sup>Disability Services Commission WA

This research 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;

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.

The above aims will be addressed via the following studies:

Towards Prevention – A Population Health Approach to Child Abuse and Neglect: A Measurement Model and the Identification of Antecedent Causal Pathways

PhD candidate: O'Donnell M

Supervisors: Kendall G, Stanley F, Leonard H, Patterson Y, Mathews R

1. Develop a population-based measure of child abuse and neglect that can be used to monitor trends in WA over time and make national and international comparisons.
2. Use the population-based measure to identify children in Western Australia who experience health outcomes that are indicative of abuse and/or neglect and compare this information to Department for Community Development (DCD) care and protection data.
3. Describe the physical, psychological and social characteristics of abused and/or neglected children, their family and community of residence for the non-Aboriginal and Aboriginal population.

Changing socioeconomic inequalities in perinatal, infant and childhood health and developmental outcomes

PhD candidate: Langridge AT

Supervisors: Kendall G, Li J, Zubrick S, Codde J

1. Examine the validity and predictability of SEIFA as a socio-economic determinant of health.
2. Develop two indices (one for Aboriginal populations and one for non-Aboriginal populations) using Census variables available from the ABS, to measure changes in socioeconomic inequalities over time.
3. Expand existing knowledge on how changes in socioeconomic inequalities have affected perinatal, infant and childhood health and developmental outcomes.
4. Identify core indicators that could be routinely collected at population level, to help in the monitoring of future changes in socioeconomic inequalities

Exploring developmental pathways to health and education, in order to inform early intervention policies

PhD candidate: Malacova E

Supervisors: Li J, de Klerk N, Leonard H, Humphry S

1. Identify mechanisms that underpin social gradients in educational achievement.
2. Contribute to a better understanding of the impact of multi-level risk and protective factors on numeracy and literacy in primary school children.
3. Establish if and how much adverse birth outcomes and poor health in early and mid-childhood are significant contributing factors to poor educational outcomes in socially disadvantaged children.

How the relationship between Aboriginal Australians and Anglo-Celtic Australians mediates the success of WA State Government policies, programs and services provided to Aboriginal families

PhD candidate: Pearson G

Supervisors: Freemantle J, Vicary D, Silburn S, Kickett-Tucker C

1. Develop a contextual framework that describes the elements of the current relationship, its evolution, application and the culture(s) that these exist within,

2. Identify the types of relationships that are more conducive to promoting better more meaningful interactions between the two groups,

3. Identify elements that are specific to the relationship between Anglo Celtic Australians and Aboriginal Australians, and

4. Develop an instrument that "measures" the relationship between Anglo Celtic Australians and Aboriginal Australians

Impact of abuse and/or neglect that has resulted in care and protection: effect on mental health and developmental outcomes in adolescence and early adulthood

PhD candidate: Northey K

Supervisors: Kendall G, Li J, Silburn S

1. Describe the pattern of risk for known health and developmental outcomes during adolescence and early childhood associated with previous history of abuse/neglect that has led to contact with the child protection system (CPS).

2. Quantify the degree to which the experience of out-of-home care is related to educational developmental trajectories in literacy and numeracy at Years 3, 5 and 7

3. Quantify the way in which the dimensions of the out-of-home care a factor that is associated with mental health and developmental outcomes in adolescence

4. Determine if the age at which youth are discharged from care and protection into independent living is a factor that contributes health and developmental outcomes

5. Quantify the degree to which the experience of abuse/neglect impacts differentially depending on the socio-demographic characteristics of the child, family and community

Charting the development of offending among Western Australian children

PhD candidate: Ferrante A

Supervisors: Morgan F, Kendall G, Zubrick S

1. Use longitudinal data to chart the development of offending (delinquency) among Western Australian children

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2. Use a “criminal career” framework to describe the onset, frequency, continuity (desistance) and severity of offending over the life-course
3. Explore the characterization of offenders through different developmental trajectories.
4. Identify key risk and protective factors associated with offending factors related to the individual, family, community & environment
5. Map pathways into and out of offending and identify crucial transition points in life
6. Explore difference between Aboriginal and non-Aboriginal offending patterns

## WA Register for Autism Spectrum Disorders

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Dixon G, Glasson E, Bower C, Wray J

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 on: the number and ages of people diagnosed; the severity of disability; and shared biological, psychiatric and developmental features. Between 1999 and 2004, the Register has collected diagnostic

and demographic information for 1223 children, adolescents and some adults who were newly diagnosed with an autism spectrum disorder. Seventy-six percent of all cases were diagnosed with autism, 19% with PDD-NOS, and 5% with Asperger syndrome. The median age at diagnosis was 4 years of age (range 15 months to 50 years) and males outnumbered females with a ratio of 4.6 to 1.

Relevant references:

Williams K, Glasson EJ, Wray J, Tuck M, Helmer M, Bower CI, Mellis CM (2005). Incidence of autism spectrum disorders in children in two Australian states. *Medical Journal of Australia*, 182(3), 108-111.

Glasson E, Bolton H, Chauvel P, Cohen D, Cook H, Dixon G, Klinken J, McMullin B, Tender J, Wray J (2006). WA Register for Autism Spectrum Disorders – 2004 Report. Perth, Western Australia.

## Birth defects in children diagnosed with Autism Spectrum Disorders

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Dawson S, Glasson E, Bower C, Dixon G

Autism Spectrum Disorders (ASDs) are severe developmental disabilities that affect the way a person communicates and relates to the world around them. ASDs include autism, Asperger syndrome and Pervasive Developmental Disorders Not Otherwise Specified (PDD-NOS). They are estimated to affect two to six out of every 1000 children and each requires lifelong care and support.

The cause of ASDs is unknown, although a genetic influence is suspected. Some studies have suggested an association existing between ASDs and birth defects but as yet no published research has been designed with this specific relationship in mind.

This study is the first population based investigation to determine if there is an increased prevalence of birth defects in children with ASD.

WA population-based linked data were used to compare ASD cases (n=465) with their siblings (n=481) and population controls (n=1313) in a nested case-control study. Data on the study population, born between 1980 and 1995, were obtained from a previous study investigating ASDs and obstetric complications, the WA Maternal and Child Health Research Data Base and the Birth

Defects Registry of WA.

The results of this study found that there was a statistically significant relationship between ASDs and birth defects. The prevalence of birth defects was significantly higher in ASD cases when compared to population controls and this relationship was still significant when adjusted for confounding factors. This study also found significant findings for case-control comparisons for defects of the nervous system, uro-genital tract and the ear, face and neck. The results suggest that these defects are typical of the birth defects seen in children with ASDs, however the numbers in each category are too small to conclusively suggest any causal relationships.

This study has confirmed that ASDs and birth defects are associated, with children with an ASD almost twice as likely to have had a birth defect. This identifies birth defects as a risk factor for the development of an ASD and has implications for public health and the early detection of these disorders. It allows families and clinicians to have a greater knowledge of ASDs and awareness of factors that may increase a child's risk of developing an ASD. It may also lead to the earlier detection of these disorders which is thought to improve the effectiveness of treatment options.

#### WA Cerebral Palsy Register

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

Cerebral Palsy (CP) is a chronic neurological condition affecting movement and posture, ranging in severity from barely noticeable to severely disabling. As there is no cure, prevention and effective management are top priorities.

The WA CP Register, now in existence for 26 years, is used to monitor the occurrence of CP in WA and carry out research to investigate its causes and evaluate treatment strategies. In 2005 the Register has continued to actively ascertain new cases from multiple sources and to update information on the five-year-old cohort. Data are now complete to birth-year 1999.

#### Australian Cerebral Palsy Register (ACPR)

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

Our lack of knowledge regarding the extent and distribution of CP across Australia led to the setting up of a national collaboration to combine CP data from all States and Territories.

The ACPR has been co-ordinated by WA CP Register staff since its inception in 2002. All States and Territories subsequently agreed on criteria for a minimum data set and the location of the clearing house at TICHR, to operate as a Collaborating Unit of AIHW.

Coverage of the national live birth population has increased from 45% at the outset to more than 95% in 2005, with only the Northern Territory and Tasmania still seeking funding. An internet website donated to the NSW CP Register provides all States with facilities for data entry, management and transfer. An essential aspect of data pooling is the need to address intra- and interstate differences in classifying CP.

We are now developing a new method of recording clinical data, including the creation of motor assessment videos of children to be used for training and trialling the new form nationally. A meeting of all State and Territory representatives hosted by TICHR in May 2005 provided the opportunity for a national CP classification seminar as well as discussion of progress and data consistency issues. Both the ACPR and the Queensland Cerebral Palsy Register were formally launched during Cerebral Palsy Week in August 2005.

#### Case-control studies of cerebral palsy in term and preterm infants

Blair E, Stanley F, de Groot J, Watson L, Kurinczuk J, Petterson B, Nelson K

CP refers to a collection of conditions having in common a motor disorder due to cerebral pathology acquired early in development, therefore there are many ways in which CP may be caused. The cause of the cerebral palsy is far from clear in the majority of cases. The few causes that are fully understood can now be prevented, and are routinely prevented in developed countries.

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It is now known that less than 10% of CP cases in developed countries can be attributed to events that occur during birth. Many factors associated with cerebral palsy, such as preterm birth, multiple pregnancy, growth restriction and a variety of complications of pregnancy, nonetheless are seldom followed by CP. This has given rise to the idea that combinations of factors may be required in order to cause CP. The case control study of CP in term and preterm infants seeks to identify some of these combinations.

Antenatal and perinatal data have been collected from medical records for all children born in WA between 1980 and 1995 who are registered on the WA CP Register. Similar data have also been collected for an equal number of neonatal survivors who are not on the register, and of perinatal deaths. These comprehensive data have now been computerised and are being organised into a structure to facilitate analysis.

## IDEA (Intellectual Disability Exploring Answers) Database

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Leonard H, Bourke J, Bower C, Schiavello T, Dragovic S

The IDEA database provides population-based information on intellectual disability in WA based on medical and demographic data collected by the Disability Services Commission. 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, 2002 and 2004. 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. The database has been used on a national level to provide information to the Australian Burden of Disease and Injury Study for estimating the prevalence of intellectual disability in Australia.

Research studies using 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. A current study aims to investigate autism and intellectual disability and compare epidemiological profiles of cases over time. This study aims to determine whether changes in Autism Spectrum Disorder and intellectual disability prevalence reflect diagnostic drift, and in particular to investigate the social determinants, antenatal, perinatal and maternal characteristics of children with and without autism.

A symposium on Intellectual Disability and Autism was held in November, 2005 at the Telethon Institute for Child Health Research to present clinical and research advances around intellectual disability. This provided the opportunity for clinicians, allied health professionals, researchers and parents to interact and discuss topics such as the clinical investigation of a child with Global Developmental Delay and genetics and autism.

Advisory Council 2005: B. Petterson, C. Bower, H. Leonard (TICHR), J. Valentine (PMH), V. Morgan (UWA), R. Sanders (Dept of Education and Training), A. Mathews (DSC), K. Stopher (DSC), P. Chauvel (Consultant), J. Wray (SCDC), P. Rowe (SCDC), C. Rook (Consumer)

## Childhood Cancer Epidemiology

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

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

Researchers in the Childhood Cancer Epidemiology program have now completed the third year of a five-year (2003-2007) NHMRC funded national case-control study into the causes of childhood acute lymphoblastic leukemia (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.

The study is well under way. To date, 376 cases have been notified to us, 363 (97%) 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. 309 of the cases in remission have been invited to participate, of whom 250 (69%) have consented, 31 have declined (8%), 2 died prior

to consent and the rest are yet to consent. DNA collection is complete for 237 (95%) recruited cases, and 199 (80%) case families have completed questionnaires. To date 521 (47%) recruited control families have completed food questionnaires, and 344 (51%) have provided DNA samples. Genotyping is well underway.

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

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Milne E, de Klerk N, Kees U, in collaboration with Armstrong B (The University of Sydney), van Bockxmeer F (Biochemistry, Royal Perth Hospital), Baker D (Princess Margaret Hospital), Thompson J (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 (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 has been accepted for publication in the International Journal of Cancer.

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

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Milne E, Kees U, Bailey H, Robertson L in

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collaboration with Armstrong B (The University of Sydney), van Bockxmeer F and Brisbane J (Biochemistry, Royal Perth Hospital), Ashton L (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. A manuscript has been accepted for publication in the journal *Cancer Epidemiology, Biomarkers and Prevention*.

## Social, Economic and Psychological and Cultural Determinants of Health

Formative study of discrimination and mental health of CALD Australian children

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Runions K<sup>1</sup>, Dandy J<sup>1</sup>, Li J<sup>2</sup>, Zubrick S<sup>2</sup>, Silburn S<sup>2</sup>, Cross D<sup>3</sup>

<sup>1</sup>School of Psychology, Edith Cowan University, <sup>2</sup>Telethon Institute for Child Health Research <sup>3</sup>Child Health Promotion Research Unit, Edith Cowan University

In the wake of renewed interest in social determinants of health outcomes, the effects of racism have begun to be recognised as key contributors to mental health outcomes for African Americans.

This Healthway-funded study will provide a preliminary examination of the relationship between perceived discrimination and internalising and externalising outcomes in Culturally and Linguistically Diverse (CaLD) children (aged 8-12) of Asian and Middle-Eastern descent. A select set of potential mediators and moderators of this relationship will be piloted, including measures of attribution tendencies and ethnic identity.

This project consists of three stages. The first stage, initiated in 2005, involves the consultation of an

Advisory Group, which includes representatives from the Office of Multicultural Interests of the WA Government, the Ethnic Communities Council of WA, the Metropolitan Migrant Resource Centre, ISHAR Multicultural Centre for Women's Health, Dar Al Shifah, and the Thai Cultural Community of WA. The second stage will consist of interviews with children and their parents. The final stage will involve a pilot test of instruments modified during phases 1 and 2 to examine the covariance of key constructs.

The results of this work will support a larger research project and the development of programmes to support resilient responses to discrimination for CaLD children.

## Biopsychosocial pathways to healthy child development

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Kendall G, Zubrick S, Stanley F, Silburn S, Li J, Oddy W

Utilising data from the Western Australian Pregnancy Cohort (Raine) Study, Dr Garth Kendall 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.

## Roots of Empathy

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Kendall G, Austin R, Jacoby P, Stanley F, Schonert-Reichl K, Hertzman C (latter two University of British Columbia)

The purpose of this study is to evaluate the effectiveness of a primary preventive intervention -- the "Roots of Empathy" -- a classroom-based program designed to foster children's empathy and social competencies and reduce antisocial/aggressive and bullying behaviours. ROE was developed from both theoretical and empirical literature on the antecedents and determinants of empathy, aggressive, and prosocial (caring) behaviour in children. The program, created by Mary Gordon, was initially piloted in two classrooms in Toronto, Canada in 1996. Since that time the program has

grown to serve thousands of children and has been extended to over 1000 classrooms across eight provinces in Canada, reaching over 25,000 children. This year the program is being piloted in Western Australia and New South Wales. This is the first time the "Roots of Empathy" program is being implemented and fully evaluated outside of Canada.

Pre-test and post-test data were collected in 17 intervention schools and 12 control schools in 2005. These data for over 400 children have been entered into a database which is currently being prepared for statistical analysis.

#### A New Public Health Strategy for Children in Care: Developing a Canadian/Australian Collaboration

Stanley F, Kendall G, Li J, Zubrick S, Roos N, Bronwell M, Burnside L, Kozyrskyj A (latter four Manitoba)

This project brings together two groups with two of the richest, population-based health data infrastructures in the world, to build a program of collaborative research focusing on the health of children in provincial/state care. These are likely the most vulnerable members of our society, often victims of abuse, whom we hear about only when something catastrophic has happened. A common theme in the literature is the lack of comparative data about protected and non-protected children. As a result, important questions remain unanswered, such as: Why do children in care receive suboptimal health care when these children are clearly in need of these services? Why does maltreatment (as a common reason for entry into protection) occur in the first place and what are the potential upstream interventions that can reduce the incidence of child abuse and neglect? What are the differences in health status between protected and non-protected children, and do these differences diminish as a result of going into protection? What are some of the factors associated with positive health outcomes for children in care?

This group met at TICHR in March 2005 to plan a series of comparative papers. This collaboration has progressed significantly in 2005 and the publication of this work is imminent.

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

Mattes E

Dr 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

Mattes E

This study comprises a collaboration 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

Mattes E, Kendall G, van Eekelen A, Foster J

This study comprises a collaboration to examine the neurobiological pathways through which the social determinants operate. Specifically, it will investigate 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, using the Raine Study.

## Adolescent Development

### The Virtual Infant Parenting Program: A Randomised Controlled Trial

Silburn S, Hart B, Codde J, Brinkman S, Baxendale S, Hutton H & Steyns P

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 each of the Metropolitan Area Health Service regions were invited to take part in the VIP study and 58 schools elected to participate. The program was delivered to 1,277 female high school students between 2003 and 2005 and a further 1,553 female students were enrolled as comparison subjects.

The VIP program was delivered by School Health 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 realistically replicates the sleeping and feeding patterns of a 6- week-old infant.

### Role of Implanon (etonogestrel implants) in the prevention of repeat teenage pregnancy

Skinner R., Hickey M., Doherty D

180 pregnant adolescent subjects are being recruited to a 2 year longitudinal study evaluating the acceptability and continuation rates of Implanon contraceptive implants in this population. The role of Implanon in the prevention of repeat pregnancy will also be evaluated. Participants are surveyed at baseline and at 3 monthly intervals, collecting data on contraceptive continuation, repeat pregnancy, and sexually transmitted infections. Up until the end of 2005, 135 subjects had been recruited. Funding

is from the Raine Medical Research Foundation, the University of Western Australian and the Women's and Infants' Research Foundation.

### Biopsychosocial antecedents of repeat teenage pregnancy

Skinner R., Hickey M., Doherty D, Kendall, G.

This study is being run in parallel with the "Role of Implanon in prevention of repeat teenage pregnancy". This study aims to collect comprehensive data on the bio-psychosocial risk factors for repeat pregnancy in the teenage years and the healthy adjustment to teenage parenting. Standardised instruments are being utilized to measure functioning in a range of domains. Data collected will be compared to population norms and will also be linked to WA Data Linkage System.

### Why do so many teenagers fall pregnant?

#### Biopsychosocial antecedents of teenage pregnancy.

Skinner R, Zubrick S, Silburn, S., Kendall, G, Hickey M, Doherty D, Milroy H, Fyfe S, Fenwick, J

This 2-stage project seeks to elucidate complex biological, psychological, and social pathways to unplanned pregnancy in the teenage years. In Phase 1, perceptions, values and beliefs will be explored in a qualitative study. Aboriginal and non-Aboriginal teenagers attending antenatal, termination and family planning clinics will be interviewed. Data from these interviews will generate new hypotheses regarding pregnancy risk in this age group. In Phase 2, 600 teenagers from schools, antenatal and termination clinics will be surveyed using computerised questionnaires. They will be asked about beliefs identified as important in phase 1, and a range of other individual, family, and environmental factors identified in other studies to be risk factors for early pregnancy. Statistical analysis will be used to determine how multiple risk factors interact or combine to shape sexual and childbearing behaviour.

This study will lead to new understandings of teenage pregnancy in Australia, and more effective teenage pregnancy intervention programs. The project commenced in 2005 and will run through until 2008. During 2005, recruitment and training of

research assistants, ethics approvals and approvals from community clinics and hospitals were obtained. Recruitment of subjects will begin in 2006.

## Suicide Prevention

### WA Ministerial Council for Suicide Prevention

Silburn S (Chair), Jones J (Executive Officer), Miller K, Mudgway N, Robertson D, Sayers M, Northey K

The Institute supports a significant 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. This has been assisted by the Ministerial Council for Suicide Prevention (MCSP) being administratively based at the Institute. The Council reports through the Minister for Health to all other Ministers on the Cabinet Subcommittee for Social Policy. It is responsible for advancing scientific and community understanding of suicide prevention and advises and co-ordinates government non-government efforts to reduce the morbidity and mortality associated with suicide and self-harm. The Council includes senior representation of all government departments concerned with human services and social policy, non-government agencies, and key community stakeholders.

The Council 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. This is an important research tool which has assisted the monitoring of emerging trends, such as the recently observed association between illicit drug use and increased suicidal risk for young people.

The MCSP coordinates a program of research into the hospital and community management of deliberate self-harm. This has involved the design and maintenance of a deliberate self-harm database within each of the three adult teaching hospitals in Perth. Funding from the Australian Government's National Suicide Prevention Strategy (NSPS) has enabled the Council to conclude an 18-month study regarding the prevention, treatment and support needs of suicidal men aged 17-35 years. The

project utilised qualitative and quantitative research methods in a carer and consumer consultation process to inform and support the development and improvement of suicide intervention and prevention initiatives to reduce the high rate of suicide among men. This gathered information from men in the general population, at-risk groups, carers and service providers, totalling 591 participants. This involved development of a risk-management protocol to ensure the safe and ethical collection of information from individuals who were at known high-risk. It also entailed extensive interagency negotiation and cooperation to ensure the back-up availability of community crisis services and counselling should this be required.

This study has produced 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 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 Funded by Woodside Energy Ltd. and the Telethon Institute for Child Health Research, has developed an on-line information and resource system for professionals and the general community.

The ASPIRE (Australian Suicide Prevention information and Resource Exchange) now provides Australia-wide access to over 3,500 research articles and suicide prevention resource materials via Australia's inter-library loan system.

In 2005 the Margaret River Friends of the Institute funded the MCSP to develop and pilot an Information Resource Pack for family friends caring for a young person recovering from a suicide attempt or an episode of acute suicidal behaviour. This is the first Australian publication of its kind. It aims to address a major gap in the information resources readily available to families and friends who play such a vital role in the months and years following a suicidal crisis. There has been significant interest in this publication and funding is now being sought for it to be made more widely available throughout the State and nationally.

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## Capacity Building Grants in Population Health

Indigenous Capacity Building Grant (ICBG). Not Just Scholars But Leaders: Learning Circles in Indigenous Health Research

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

Commencing in February 2005, this NHMRC funded capacity building grant aims to build the capacity of 10 Indigenous researchers over 5 years to be able to conduct Indigenous specific population health research.

The ICBG looks to build the capacity of the team investigators by working within 4 broad and overlapping research themes. The first aims to improve the quality of relevant research, increase indigenous peoples' 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 preventative and acute care for indigenous Australians. The third theme explores life style, 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 well being.

In 2005 team investigators have had 10 publications to date that have been accepted, with a further 19 publications either already submitted or nearing submission. Other highlights for 2005 also include the 23 various presentations made by team investigators as well as representation on 21 State, National and International bodies and committees. Also awarded in 2005 was a NHMRC PhD scholarship to M. Wright who will commence his PhD program in 2006. Thus 2006 is already shaping up to be an even more exciting year than 2005 was as the solid foundations are continued to be built upon.

## Community and Consumer Participation

In 2003, the Institute was awarded jointly with the UWA School of Population Health (SPH) a NHMRC Capacity Building Grant, which enabled the shared appointment of a Consumer Research Liaison Officer between the Institute and SPH.

In 2004 a strategic plan was developed to address the multi-faceted requirements of a consumer and community participation strategy and to:

- Support the ethos of the joint National Health and Medical Research Council and Consumers Health Forum of Australia Statement on consumer and community participation;
- Expand and build on current consumer and community participation collaborations;
- Manage organisational change; and
- Address National Health and Medical Research Council accreditation requirements for TICHR.

Consumer and community participation initiatives undertaken at the Institute during 2005 have built on this long-term strategy and have included:

1. The development and implementation of an Institute wide policy on consumer and community participation at the Institute;
2. The establishment of a joint Institute & SPH Consumer and Community Participation Steering Committee;
3. Planning and development for the establishment of a Consumer and Community Advisory Council;
4. The inclusion of consumer and community participation practices in Institute projects such as the Raine Study and Rett Syndrome Project;
5. The inclusion of a budgeted component for consumer and community participation in the Foetal Alcohol Study funding application; and
6. Collaboration between the Office for Children and Youth and the Institute to establish and build on opportunities for young people to be more involved in research.

2006 will see further exciting initiatives developed and new collaborations established, all of which aim to increase and enhance consumer and community

participation and add value to research at the Institute.

## The Applied Research Projects in Child Health

Department of Health WA

### Translation Project

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Jackiewicz T, Clark K, Smith G

This research area involves a planned program of work with the purpose of encouraging and supporting the uptake of relevant research evidence and information into policy and practice in community and child health in Western Australia.

The vision for the Institute is to be a resource that can be used by the Health System to provide policy and practice relevant information and evidence to ensure best practice evidence based policy and practice in community and child health. The overall intent of the proposed program of work is to position the Institute as a leader and expert in the application and provision of research information to Community and Child Health Services in Western Australia. It is anticipated that this program of work will lead to long term relationships with the Department of Health and its Health Services and will generate the production of good quality useful research information on a range of relevant priority health issues.

Work in 2005 involved the planning stages of this new research area. This planning involved the preparation of a number of reports outlining the justification for a focus on evidence based policy and practice and research proposal for the collection of baseline information from Health Services regarding their research utilization practices and how the ICHR can better target information and evidence that leads to changes in policy and practice. As part of this project, ICHR has partnered with the North Metropolitan Health Service to assist in researching the evidence base for breastfeeding initiation and retention rates in Western Australia with the aim of developing a strategic agenda for the promotion of exclusive breastfeeding until 6 months. This project is ongoing.

Early Years Evaluation: An examination of the overarching theoretical basis for community based interventions in the early years.

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Clark K, Robson A, Jackiewicz S and Jackiewicz T

This project involved the preparation of a report for health service managers and field staff that aims to guide the design and implementation of early years programs and services. The report is intended to address common challenges in the design and delivery of early years programs. The report draws on the experience of ICHR that has been gained through involvement in early years program evaluations and from published literature on early years program delivery. The paper is expected to play a part in ensuring that local early years initiatives are delivered in ways that produce better outcomes for children and families. The project is ongoing.

### Chronic Disease Plan

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James R

This project involves ICHR providing advice to Department of Health on chronic disease prevention strategies in the context of health promotion services. It also involved the building of capacity within the Department of Health to implement chronic disease prevention initiatives as well as population health staff in regions to respond to the Chronic Disease Prevention Strategy.

This project also involved a number of stakeholders including National Heart Foundation, Cancer Council, Health Reform Committee, Curtin University, Australian Health Promotion Association, WA Country Health Services and Population Health Directors. A review of Literature on Change Management was undertaken and presented to relevant officers. This project ended in June 2005.

### Uniform Health Promotion planning and evaluation project

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James R

This project will help create a consistent and uniform process for health promotion program planning and evaluation in all regions in WA. This process is managed by a reference group of

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representatives including those from the TICHHR as well as the Health Promotion Directorate and the WA Research and Evaluation Network. As part of this project, a review of literature on program planning and evaluation has been prepared including a review of existing material from regions on program planning and evaluation. Institute staff provided regular dispatches of evaluation literature and case studies for regional population health officers, the research and evaluation network and directors of population health. This project ended in June 2005.

## Recruitment Strategy for Virtual Infant Parenting Program Research Trial

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Williams A

The Virtual Infant Parenting (VIP) program is a school based health promotion program where teenage participants learn about pre-conceptual health, pregnancy, childbirth and the practical realities of caring for a young infant. The task was to develop and implement a revised recruitment strategy to support the Virtual Infant Parenting Project Research Trial in the North Metropolitan Health Region. The Recruitment Officer undertook to review the grant proposal, the community nurse workshop report and all project materials and products to ascertain perceived barriers to recruitment. As a result of the recruitment strategy, recruitment numbers increased from 365 to 730 students, increasing overall participation rates in the time frame from 25% to 33%. The major barrier constraining the initiative was the need to re-contact parents and students and ask once again for consent in spite of their previous decline to participate or failure to respond to the request for signed consent. In the two schools where this was not so, and students were recruited en masse as year groups, recruitment rates were 33% and 46% respectively. Outputs from this phase of the project will subsequently inform recruitment strategies in newly assigned areas, and inform future interventions trials in school settings. This project ended in June 2005.

## Girradoola Pathways Evaluation

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Clark K, Jackiewicz S

This project is directed to the broad area of maternal and child health and wellbeing, which is a policy priority for all Australian State and Commonwealth Governments. The Girradoola Pathways Project is an early intervention program targeting 0-5 year old children in the Girrawheen and Koondoola suburbs of Perth. It is joint initiative of Mission Australia (MA) and The Smith Family that is delivered by MA staff in partnership with The Department of Education and Training (in local schools) and the Girrawheen-Koondoola Communities.

The evaluation support provided to this program included the establishment through a series of workshops of Program Logic for the program, preparation and provision of an evaluation plan and consultancy on establishing mechanisms to ensure collection of good quality data to ensure successful assessment as to the effectiveness of the program.

## Commonwealth Department of Family and Community Services

### Phase I of Longitudinal Study of Australian children: Parenting and Families in Australia.

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Smith G, Zubrick S and Jackiewicz T

This project involves analysis of data from Phase I of Longitudinal Study of Australian Children (LSAC) to produce the theme report "Parenting and Families in Australia". Data analysis is currently underway.

The final report will include discussion on the following themes:

1. Parenting styles, roles, and family functioning - This theme will explore how each parent perceives their role in the family (i.e. as the primary care giver, financial provider) and how this influences their parenting style and affects the functioning of the family unit.
2. Parents' feelings about parenting - The factors that may influence parents' feelings towards parenting are to be investigated.
3. Support for Parents - This part of the research paper will explore how parents perceive their

neighbourhood, government and other services and support available to them in their community more generally, and the influence this has on their parenting behaviours and their child's outcomes.

4. Non-Resident Parents (NRPs) - This theme is focussed on the nature of the non-resident parents' involvement with their infants and 4–5 year olds.

Data analysis is currently underway and will continue into the first half of 2006.

### Indigenous Child Care Plan

Jackiewicz S

The National Indigenous Child Care Plan is a collaborative project between Edith Cowan University, the Telethon Institute for Child Health Research and other organizations. The project is funded by the Commonwealth Department of Family and Community Services. The National Indigenous Child Care Plan will be used by FaCS to guide the development of any new and existing Indigenous Child Care services. The approach used in this project is strengths based, building upon strengths of communities and individuals. Consultations with Indigenous child care providers and community members have been conducted in each State and Territory. Government representative from Federal and State departments have been consulted in each State or Territory. In addition to the consultations both the national and international literature has been reviewed to inform the plan. The development of the plan will be based on findings from the consultations, work completed in the past by organisations in Australia such as Secretariat of National Aboriginal and Islander Child Care (SNAICC) and others, as well as Australian and international literature. This project is due for completion in 2006.

Other projects - The Smith Family

Evaluation of the Mirrabooka and Kwinana Community for Children Initiatives

Clark K, Jackiewicz S

The Commonwealth's Communities for Children (C4C) Program (Community for Children Initiative) funds large community organisations to develop

and implement a whole of community approach to children and families focusing on: healthy young families; early learning and development; supporting families and parents; and child friendly communities. The Commonwealth has provided funding to The Smith Family for the purpose of carrying out the objectives of the Program.

ICHR's involvement in the project involved the development of a Program Logic/Evaluation Framework for each of the Mirrabooka and Kwinana C4C funded interventions including a series of workshops and the development of program documentation as applicable for each Initiative. The Institute also provided consultancy services to the Mirrabooka and Kwinana C4C Initiatives addressing issues such as development and collection of baseline data for each Initiative, use and interpretation of data collected as a result of the implementation of the program logic, use of early years research to guide service development and delivery, data collection methodology and implementation. The project also involved the guiding of the development of the Kwinana Initiative in developing its Community Action Plan and Service Delivery Plan as a result of available early year's research.

## Centre for Developmental Health

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 which has operated since June 2001. This multidisciplinary centre brings 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. This 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

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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. This perspective offers a systematic means of informing action to address the underlying social, economic and other environmental factors that determine disparities in children's health and development.

Over the past four years the Centre has built a national and international profile in academic research and policy in promoting children's developmental health. It has established strong links with government and other agencies responsible for the health, education and wellbeing of children in Western Australia, and Australia.

One of the main accomplishments of the Centre during 2005 was its success in winning a \$1.3 million NHMRC "Healthy Start to Life" grant for the period 2006 to 2010 to develop and evaluate a community-based program for Aboriginal parents to build strong families and assist children to have a healthy start in life. The Restor(y)ing Aboriginal Parenting Project targets parents of children aged 12 – 36 months, to support them in promoting their children's behavioural and social competence and readiness for school learning. The program will initially be tailored to the needs of Aboriginal families in the Perth metropolitan area and other regional urban centres in WA.

Findings from focus group consultations with Aboriginal parents and service providers, and data from the WA Aboriginal Child Health Survey will help in identifying modifiable risk and protective factors associated with parenting and children's behavioural and emotional wellbeing and the development of a group parent program to promote children's early development and competencies in ways which will prepare them for success at school.

The project is being implemented in conjunction with the Kulunga research network. The project team comprise principal investigators Prof Steve Zubrick, Prof Sven Silburn, Prof Rob Donovan, Heather D'Antoine, A/Prof Helen Milroy, A/Prof Ted Wilkes, Dr David Lawrence and Dr Cheryl

Kickett-Tucker; Associate Investigators Adele Cox and Glenn Pearson, and project manager Anwen Williams.

## The Australian Early Development Index (AEDI): Building Better Communities for Children

Prof Sven Silburn (ICHR), Sally Brinkman and Dr Bret Hart (North metro area health service), Prof Frank Oberklaid, Dr Sharon Goldfeld, Mary Sayers and Alex Fraser (Centre for Community Child Health, Melbourne).

The AEDI is an adaptation of a Canadian measure of early child development and readiness for school learning which enables communities to assess the proportion of children in their first full-time year of school who are 'developmentally vulnerable' in terms of five areas of early child development: a) physical health and wellbeing, b) social competence, c) emotional maturity, d) language and cognitive skills, and e) communication skills and general knowledge social competence.

Children are considered to be 'developmentally vulnerable' if their AEDI score on one or more domains is below the 10th percentile of compared with all children across Australia who have participated in the project. The first phase of the AEDI project involved refining and adapting the instrument for use with Australian children. It also involved establishing a national support centre and a secure on-line data entry facility to enable communities throughout Australia to implement the AEDI process.

In the current phase of the project, 933 teachers in 430 primary schools around Australia recorded information on over 16,756 children. This enabled summary reports to be produced for each of the 25 participating communities. These provide a demographic profile of the community and describe how children are doing on each of the AEDI domains of child development. The participating communities are now being supported to utilise their findings to map services needs and community resources for children and families and to use this for initiating community action and services to address identified needs.

The AEDI is funded by the Australian Government

Department of Family and Community Services with corporate support from Shell Australia. More information on the project is available at <http://www.australianedi.org.au> The AEDI, an initiative of the Centre for Community Child Health (CCCH) (a key research centre of the Murdoch Children's Research Institute) in partnership with the Telethon Institute for Child Health Research (TICHR).

The AEDI is a powerful tool for creating communities where all children can thrive and grow to fulfil their potential. It assists communities to understand how their children are doing in crucial areas of development such as physical health, language and communication, emotions, behaviour and social competence. Communities can use their results to put effort and resources into services and programs for young children so that all children make the best possible start as they enter primary school.

Findings of the AEDI were announced in Broadmeadows, Melbourne in November 2005, by the Minister for Family and Community Services, Senator Kay Patterson.

# Division of Population Sciences

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# Division of Population Sciences

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D McAullay PhD candidate ANU  
 M Measey BVSc, MPH, PhD candidate  
 S Mirshahi PhD candidate, Centre for International Health, Curtin University of Technology  
 H Monteiro BA SocSci, MPH candidate  
 A Mullan  
 M O'Donnell BPsych, MPsych, DipEd, PhD candidate  
 G Pearson Masters candidate UWA  
 N Pingault BSc(MedSci)(Hons I), MASM, MAIMS, PhD candidate  
 W Pomat BSc(Hons), MSc, PhD candidate  
 K Ward RMHN, BAppSci (Psych), MSc (Public Health), PhD candidate  
 F Watt B.Psych M.Science candidate

■ Honorary Research Fellows

Dr N Badawi MBBChE (Hons), MSc, PhD, DCH, MRCP(I) FRACP  
 Dr S Brinkman  
 Prof P Burton  
 Dr S Byrne DPhil(Oxon) MPsych/PhD BSc (Hons) DipEd BA (Hons), NHMRC Research Fellow  
 Dr J Codde  
 Dr M Croft BAppSc, PhD  
 Dr S Eades  
 Dr D Forbes  
 Dr B Hands  
 Associate Professor N Henley PhD  
 Professor D Johnson  
 Prof J Kurinczuk  
 A Mahoney  
 M Miller BSc(Hons), MAppSci, GradDipDiet, GradDipPublicAdmi  
 Dr L Nagarajan  
 Professor J Newnham  
 Dr W Oddy BAppSci, MPH, PhD  
 Dr B Petterson

Dr D Ravine MBBS., DM, FRACP, MRCPPath, FRCPA  
 Dr P Richmond  
 Dr D Silva MBBS, MPH, FRACP  
 R Skinner  
 Dr L Slack Smith  
 E Tursan d'Espaignet  
 V Vohma BSc(Hons)

## Theses passed

F Broomfield. The University of Western Australia 2005. A laboratory based test of affect regulation theory in overeating  
 K Carville. Masters in Applied Epidemiology, National Centre for Epidemiology and Public Health  
 S Dawson. B Health Sci, UWA 2005. Birth defects in children diagnosed with Autism Spectrum Disorders  
 B Hulme. The University of Western Australia 2005. Childhood overweight and bullying  
 R Jamieson. The University of Western Australia 2005. The transfer of weight and shape concern from mothers to their children  
 E Klaric. The University of Western Australia 2005. The role of parenting style in childhood obesity  
 A Lampard. The University of Western Australia 2005. Factors influencing parental concern of their child's weight.  
 C Lynch. The University of Western Australia 2005. Maternal depression and childhood obesity  
 K Miller. Master of Health Promotion 2005 - Understanding help seeking behaviours in high risk males 17-35 years in the Perth Metropolitan area.

## Awards

K Allen. Commonwealth Post-Graduate Research Scholarship  
 Clinical Professor C Bower. NHMRC Principal Research Fellowship 2005-2009  
 L Colvin. Australian Postgraduate Research Award  
 Dr J Freemantle. Healthway Public Health Post-

# Division of Population Sciences

doctoral Research Fellowship.

Dr J Freemantle. QANTAS New Investigator Travel Award

Dr I Laing. Community Health and Tuberculosis Australia Research Fellowship (Ann Woolcock Australian Fellow), 2005-2008

A Langridge. Australian Postgraduate Award Industry Scholarship

E Malacova. Australian Postgraduate Award Industry Scholarship

M O'Donnell. Australian Postgraduate Award Industry Scholarship

Dr W Oddy. NHMRC Population Health Career Development Award, 2005 - 2009

R Param. NHMRC Aboriginal and Torres Strait Islander Health Research Training Scholarship

G Pearson. Australian Postgraduate Award Industry Scholarship

A Stokes. Fiona Stanley Medal 2005

## Visitors

Professor T Achenbach

Dr N Badawi MBBChE (Hons), MSc, PhD, DCH, MRCP(I) FRACP

Dr M Croft BappSc, PhD

Dr E d'Espaignet PhD (ANU); MS (Hawai'i); MPH (Sydney); MA (Macquarie); BA (Macquarie)

J Denyer Cardiff University (Wales)

Professor L Dubois Canada Research Chair of Population Nutrition and Health Research Institute in Population Health, University of Ottawa, Ottawa, Ontario, Canada Visit: March/April 2005.

J Francis Papua New Guinea Institute of Medical Research

Dr S Fyfe BSc, BEd (Hons), BAppSc (Hons)

G Griffin

Dr E Haan

Dr C Hagquist Visiting fellow

Professor W Hall Visiting fellow

Associate Professor N Henley

Dr C Hertzman University of British Columbia

K Jones B.A (Hons)

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

H Milroy

F Mitrou BEc

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

Professor M Rice University of Kansas

C Shepherd BEc

H Wright

## External Committees

### ■ State

Clinical Professor C Bower. WA Perinatal and Infant Mortality Committee Member 1993-

Clinical Professor C Bower. WA Confidentiality of Health Information Committee, deputy member 2003-

Clinical Professor C Bower. Scientific Sub-Committee of the Human Research Ethics Committee, Curtin University of Technology 2000-

Clinical Professor C Bower. Western Australian Genetics Council, Department of Health WA, 2001-

Clinical Professor C Bower. Prenatal Diagnosis Committee, Department of Health WA, 2001-

- Clinical Professor C Bower. Western Australian Neurosciences, Foundation Member of Board, 2005-
- K Butler. WA Aboriginal Health Promotion Strategy Working Group (2004-2005)
- A Cox. Aboriginal Early Years Strategy, WA Department of Health, (2005- )
- A Cox. Aboriginal Suicide Prevention Steering Committee, Ministerial Council for Suicide Prevention, (2004- )
- A Cox. WA National Suicide Prevention Strategy Advisory Committee, Department of Health and Ageing, (2005- )
- A Cox. WA State Forensic Mental Health Service Board, (2005- )
- Dr J Freemantle. Ministerial Advisory Council on the Prevention of Death of Children and Young People (WA) 2003-
- Dr J Freemantle. Mortality Review Committee (Princess Margaret Hospital WA) 2002-
- Dr J Freemantle. Fellow of the Guildford Grammar School Council \_ Diocese of Perth nomination (2002-).
- Dr J Freemantle. Examining Chaplain, Anglican Church of Australia, Western Australia (2002- )
- Dr J Freemantle. Member Executive St George's Cathedral Foundation of the Arts (1998- )
- Associate Professor C Hayward. WA State Training Board (2005- )
- Associate Professor C Hayward. Child Deaths Advisory Committee (2004 - )
- Dr D Lehmann. Vaccine Impact Surveillance Network Committee, WA, (1998 -)
- Dr D Lehmann. Meningitis Centre Committee (1998-)
- Dr D Lehmann. Princess Margaret Hospital Ethics Committee (2005-)
- Dr D Lehmann. Perinatal and Infant Mortality Committee, Ministry for Health, WA (2005-)
- Dr E Milne. Research Committee of Cancer Council of WA (2005-)
- Dr E Milne. Confidentiality of Health Information (CHIC) Committee, WA Dept of Health, 2003-
- Dr E Milne. Cancer Foundation of WA Skin Cancer Control Steering Committee, 2001-
- Dr W Oddy. Chairperson, Baby Friendly Hospital Initiative Advisory Committee (WA) (2003-).
- Dr W Oddy. Chairperson, Breastfeeding Public Health Promotion Campaign, North Metropolitan Health Service, Western Australia (2005-)
- Dr W Oddy. Chairperson and Convenor of Breastfeeding Research Symposium, North Metropolitan Health Service Breastfeeding Update with child health nurses, Graylands Hospital, November 2005.
- Dr W Oddy. Examiner, Graduate Studies Research Committee, Division of Health Sciences, Curtin University of Technology 2005-2006
- R Param. WA Aboriginal Health Promotion Strategy Working Group (2005- )
- National
- Clinical Professor C Bower. Australian Birth Defects Society Committee member 1999 -
- Clinical Professor C Bower. Australian Paediatric Surveillance Unit Scientific Review Panel 1998-
- Clinical Professor C Bower. Australian Paediatric Surveillance Unit Board 1998-, Chair (2003-)
- Clinical Professor C Bower. National Child Health Information Advisory Committee (AIHW) 1998-
- Clinical Professor C Bower. National Perinatal Statistics Unit, National Birth Anomalies Steering Committee member 2004-
- 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)
- A Cox. LSIC Design Sub-committee, Department of Families, Communities and Indigenous Affairs (2004- )
- A Cox. LSIC Steering Committee, Department of Families, Communities & Indigenous Affairs (2004- )

# Division of Population Sciences

Dr J Freemantle. National Vice-President (policy) Public Health Association of Australia (1999 - )

Dr J Freemantle. Infant and Child Mortality and Morbidity Committee (Victoria) (Observer) 2004-

Dr J Freemantle. Child and Youth Health Intergovernmental Partnership (CHIP) of the National Public Health Partnership (2003-2005)

Dr J Freemantle. Aboriginal and Torres Strait Islander Working Group of CHIP (2003-2005)

Dr J Freemantle. Scientific Advisory Council SIDS and Kids (2003- )

Dr D Lehmann. Member of the Data Safety Monitoring Board for the Maternal pneumococcal immunization study in the Northern Territory ('PneuMum')

Dr W Oddy. Baby Friendly Hospital Initiative National Advisory Committee (2003-).

Silburn, S. Member of Consortium Advisory Group, "Footprints in Time" National Longitudinal Study of Australian Children. 2002-current

Silburn, S. Member, Design sub-committee, National Longitudinal Study of Indigenous children. 2004-current

Silburn, S. Chair, WA Ministerial Council for Suicide Prevention. 2001-current

Zubrick, S. Member, National Children and Youth Advisory Committee, Australian Bureau of Statistics, (2003 - present)

Zubrick, S. Member, Mental Health Promotion & Prevention Working Party, Commonwealth Department of Health & Aged Care, (1998 - present)

Zubrick, S. Chair, Management Committee, AUSEINET: An initiative of the National Mental Health Strategy, Mental Health Promotion, Prevention and Early Intervention (2000 – present).

Zubrick, S. Member, Australian Council for Children and Parenting, (2005 – present)

Zubrick, S. Member, Editorial Board of the Journal of Family Studies, La Trobe University, Victoria, 2004-present.

## ■ International

Clinical Professor C Bower. International Clearinghouse for Birth Defects Surveillance and Research. 2004 -, Secretary (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

Dr W Oddy. Nominated Executive Committee Member, International Society for Research into Human Milk and Lactation, 2006

Dr W Oddy. Treasurer, Conference Organising Committee, (Conference to be held in Perth 2008) International Society for Research into Human Milk and Lactation (2005-2008)

## Invited presentations

Bell L, Byrne S, Jones TW, Davis EA. Complications of childhood obesity: prevalence in a random cross-section of primary school children. Paper presented at the RACP Annual Scientific Meeting, 8-11 May 2005, Wellington NZ (2005)

Bell L, Byrne S, Thompson A, Ratnam N, Blair E, Bulsara M, Jones TW & Davis EA. Increasing childhood BMI is linearly associated with complications and co-morbidities of overweight. Poster presented at the European Society for Pediatric Endocrinology, Lyon France, September 2005.

Bell LM, Thompson AM, Byrne S, Watts K, Jones TW, Davis EA. Complications of childhood obesity: prevalence in a random sample of primary school children. Australasian Association for the Study of Obesity National Conference, Adelaide. (2005)

Clinical Professor C Bower. FAS research in Australia: where we're at and where we're going. Australian Paediatric Surveillance Unit Symposium on FAS. Sydney, March 2005.

Clinical Professor C Bower. What do we know about alcohol in pregnancy and its effects in Australia? Australian Birth Defects Society Conference,

Melbourne, April 2005

Clinical Professor C Bower. Progress in mandatory folate fortification in Australia. Australian Birth Defects Society Conference, Melbourne, April 2005

C Bower. What do we know about alcohol in pregnancy and its effects in Australia? Fetal Alcohol Syndrome Workshop: Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Behaviours and Prevention, The Children's Hospital at Westmead, Sydney, May 2005 (Invited)

Dr S Byrne. Cognitive-behavioural treatment of obesity in adults. Keynote address. National Australian Association of Cognitive-Behavioural Therapy Conference, Melbourne. (2005).

Dr S Byrne. Treatment of childhood obesity. Proceedings of the 6th National Paediatric Physiotherapy Conference, Western Australia, 45-46. (2005).

Byrne S, Watts, K., Bell L. & Davis E. Childhood obesity- Have we missed the boat? Invited symposium presented at the 6th National Paediatric Physiotherapy Conference, Perth Western Australia (2005).

Byrne SM. Cognitive-behavioural treatment of obesity in adults. Workshop presented at the National Diabetes Association Conference, Perth, W.A. (2005)

Byrne SM & Dove E. The UWA Weight management programme: Group Cognitive-behavioural treatment of obesity in adults. Invited workshop presented for the Australian Dietitians' Association. (2005).

Byrne SM, Blumberg D, Wake M & Dibley M. What childhood and adolescent obesity research questions remain to be addressed through longitudinal research? Australasian Association for the Study of Obesity National Conference, Adelaide. (2005).

Byrne, S.M. & Brennan, L. Cognitive-behavioural treatment of obesity in children, adolescents and adults. Workshop presented at the National Australian Association of Cognitive-Behavioural Therapy Conference, Melbourne. (2005).

H D'Antoine. FAS in Indigenous Australians. Fetal Alcohol Syndrome Workshop: Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Behaviours and

Prevention, The Children's Hospital at Westmead, Sydney, May 2005. (Invited)

Davis EA, Thompson AM, Watts K, Bulsara M, Byrne S, Jones TW, Bell LM. Increasing adiposity: continuum of effect on the complications and comorbidities of obesity in childhood. Australasian Association for the Study of Obesity National Conference, Adelaide (2005).

Dr J Freemantle. Overview of mortality in WA 1980-2003. School of Population Health, University of Melbourne Seminar series. 2005

Dr J Freemantle. "Chance favours the Prepared Mind". Inaugural Learning from Leaders Lecture, Ormond College, University of Melbourne. April 2005

Dr J Freemantle. Cannabis, alcohol and other drugs and road crash deaths, Western Australia 1998-2002: what are the data telling us? Injury Control Council of WA, seminar series. July 2005

Freemantle J, deKlerk N, Read A, Stanley F. Stories from the Western Australian Mortality Database. Confidential Enquiry into Maternal and Child Deaths, January 2005.

Freemantle J, Read, A., DeKlerk, N., McAullay D., Anderson I., Stanley, F. Let the data speak! Stories from the Maternal and Child Health Research Database. Seminar Series School of Population Health, University of Melbourne. October 2005

Freemantle J, Read, A., DeKlerk, N., McAullay D., Stanley, F. "...but not in vain!" How data are being used to prevent death in infants, children and young people in WA. Key note address to Coroners Conference of Australasia, November 2005

Freemantle J, Read, A., DeKlerk, N., Stanley, F., McAullay D., Doyle, A. The rate of SIDS decrease in Western Australia....."Have we really got the right picture? National symposium SIDS and Kids, Adelaide March 2005

Freemantle J. de Klerk, N., Read, A. Who gives a puff? Population data describing the outcomes of smoking in pregnancy in Western Australia 1980-2002. Presentation to the National Advisory Group on Smoking and Pregnancy. December 2005.

Freemantle, J. de Klerk, N., Read, A., Divitini, M., Blair, E, McAullay D, Stanley F. Trends and patterns

# Division of Population Sciences

of mortality in WA infants and children, 1980-2002. Presentation to the NSW Child Death Review Team, June 2005

Fursland A. & Byrne, SM. A new initiative in Western Australia: The story so far on the first state-wide eating disorders service for adults. Paper presented at the Australian and New Zealand Association for eating Disorders National Conference, Sydney. (2005)

Gibson L, Byrne SM & Davis EA. Do obese children come from dysfunctional families? Australasian Association for the Study of Obesity National Conference, Adelaide. (2005)

Associate Professor C Hayward. Advocacy Workshop. 36th Public Health Association of Australia Annual Conference, Perth 2005

Associate Professor C Hayward. 2nd Year Medical Students. University of WA, Perth 2005.

Associate Professor C Hayward. State Aboriginal Health Forum, Perth 2005.

Associate Professor C Hayward. Rotary Club of Australia, Perth 2005.

Associate Professor C Hayward. Walk, Talk, Work Together. Commonwealth/State Aboriginal Health Workshop, Perth 2005

K Officer, J Freemantle. The Power of the Organised Voice – a “how to” guide to advocacy. Key note address to the Community Nurses Association AGM November 2005

Dr D Lehmann. Update on the Kalgoorlie Otitis Media Research Project, Goldfields Ear Health Conference, Kalgoorlie, WA. October 2005.

Dr E Milne. Data Linkage: a Population-based Resource, United Kingdom Childhood Cancer Study Conference, London, April 2005.

C O'Leary. Policy for the prevention of FAS in Australia and Overseas. Fetal Alcohol Syndrome Workshop: Diagnosis, Epidemiology, Behaviours and Prevention, The Children's Hospital at Westmead, Sydney, May 2005. (Invited)

C O'Leary. Fetal Alcohol Syndrome. Department of Community Development, Early Years Seminar, Perth, May 2005. (Invited)

C O'Leary, D'Antoine H Fetal Alcohol Syndrome.

Department of Community Development, Early Years Strategy, Perth, May 2005. (Invited)

Dr W Oddy. Curtin University of Technology, Developmental Health Unit, Invited lecture on 'Impact of breast milk on infant and child health'. July 2005.

Dr W Oddy. The immunological advantage in the prevention of infections and allergy Breastfeeding: Excellent Nutrition, the Evidence. 9th Congress of the Asian Pan Pacific Society of Paediatric Gastroenterology, Hepatology and Nutrition (APPSPGHN), in conjunction with the 27th Congress of the Malaysian Paediatric Association Kuala Lumpur, June 2005.

Dr W Oddy. College of Lactation Consultants, South Australia. The impact of breast milk on infant and child health, Breastfeeding and asthma in children, Breastfeeding and cognitive development in infants. October 29th, 2005, Adelaide, South Australia.

Dr W Oddy. Rett Syndrome Workshop for Parents “The experience of mealtimes in girls with Rett syndrome”. Australian Paediatric Surveillance Unit, Children's Hospital at Westmead, November 2005.

Dr W Oddy. College of Lactation Consultants Seminar, WA. Update on Breastfeeding and childhood asthma, Perth WA October 17th 2005.

Dr W Oddy. Chairperson and Convenor of Breastfeeding Research Symposium, North Metropolitan Health Service Breastfeeding Update with child health nurses, Graylands Hospital, November 2005.

Dr W Oddy. Invited lecture 'Infant and toddler nutrition' Food & Nutrition in Public Health 750.208, School of Population Health, University of Western Australia, August 2005.

Dr W Oddy. Rotary Club of Karrinyup, WA. “Omega-3 fatty acids and health” March 2005.

Dr W Oddy. Lactation Training Program, Baby Friendly Hospital Initiative, St John of God Hospital, Perth Western Australia, July 2005.

R Param. 3rd Year Medical Students. University of WA, Perth 2005.

R Param. Aboriginal Child Health. Marr Mooditj Aboriginal Health College, Perth 2005.

- R Param. Australian Early Development Index community workshop, Perth 2005.
- J Payne. Fetal Alcohol Syndrome. Women's Christian Temperance Union of WA Inc, Guest Afternoon, Perth, August 2005. (Invited)
- Payne J, Bower C, Elliott E, Haan E. Fetal Alcohol Syndrome. Antenatal Chemical Dependency Clinic, King Edward Memorial Hospital for Women, Subiaco, April 2005. (Invited)
- G Pearson. Walk, Talk, Work Together. Commonwealth/State Aboriginal Health Workshop, Perth 2005.
- Silburn, S. Western Australian Aboriginal Child Health Survey – Implications for policy and practice. 3 November 2005. 2005 Divisions of General Practice Network Forum, Perth,
- Silburn, S. The Western Australian Aboriginal child Health Survey: Are there any policy implications? 20 September 2005. Imagining Childhood – Children, culture and Community – Children are our future. Charles Darwin Symposium Series 2005, Alice Springs.
- Silburn, S. The Western Australian Child health Survey, WAACHS. Findings from Volume Two, the Social and Emotional Wellbeing of aboriginal Children and Young People. 31 August 2005. THEMHS Conference: The Mental health Services Conference Inc. of Australia and New Zealand, Adelaide.
- Silburn, S. Resources and contexts for child development: Implications for children and society. 20-22 July 2005. Australian Social Policy Conference 2005 Looking Back Looking Forward A Quarter Century of Social Change, Sydney.
- Silburn, S. The Social and Emotional Wellbeing of Aboriginal Children and Young People. 25 May 2005. Invited seminar presented at the 40th Congress of the Royal and New Zealand College of Psychiatrists, Sydney.
- Silburn, S. The Mental Health of Aboriginal Children. 22-26 May 2005. Psychiatry in a Changing World Royal Australian and New Zealand College of Psychiatrists 40th Congress, Sydney.
- Silburn, S. Suicide, drugs/alcohol/mental health problems and prevention. 24-25 February 2005.
- Comorbidity Issues for Young People, Invited keynote address to the Mental Health Services Summer Forum, Sydney.
- Silburn, S. The Australian Early Development Index, building better communities for children. 9-11 February 2005. Invited conference to present this paper at the Families Matter, 9th Australian Institute of Family Studies Conference Theme: Evidence based approaches to children's policy, Melbourne.
- Silburn, S. Mental health for Indigenous adolescents – Results from 2nd findings "social and Emotional Well-being of aboriginal children and Young People. 16 November 2005. 15th annual Australasian Coroners Society Inc Conference 2005, Perth.
- Watt F, Byrne S, Blair E, Pereira-Gale J, Davis E, Watt F, Blair E & Davis EA. Measures of adiposity for predicting mental health outcomes. Australasian Association for the Study of Obesity National Conference, Adelaide. (2005).
- Watts K, Byrne S, Thompson A, Bell L, Jones T, Davis EA. Waist girth is strongly associated with cardiovascular risk factor profile in primary school-aged children. Australasian Association for the Study of Obesity National Conference, Adelaide (2005).
- Watts, K., Allen, K.L., Gibson, L., & Byrne, S.M. Psychological aspects of childhood obesity. Symposium presented at the National Australian Association of Cognitive-Behavioural Therapy Conference, Melbourne. (2005).
- Watts, K., Gibson, L., Watt, F. & Thompson, A. Food for thought. Invited address. Public Community Forum, City of Fremantle. (2005).
- Zubrick, S. The Longitudinal Study of Australian children-Symposium and Parental separation and child mental health across the life course. 9-11 February, 2005. Families Matter: 9th Australian institute of Family Studies Conference, Keynote address, Melbourne.
- Zubrick, S. Human capability and the mental health of Aboriginal Children: Pathways towards success. 25-28 September 2005. 36th Public health Association of Australia Annual Conference Successes in Public Health, Perth.
- Zubrick, S. Resources and contexts for child development: implications for children and society.

# Division of Population Sciences

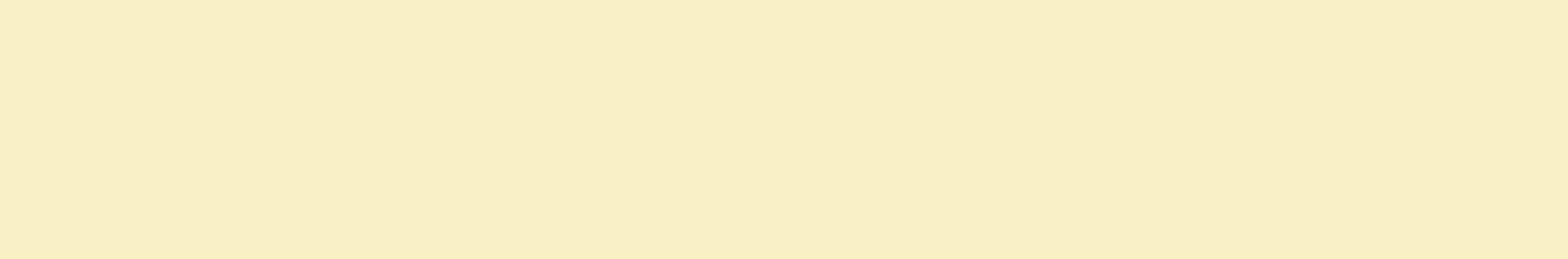
20-22 July 2005. Australian Social Policy Conference 2005, Looking Back Looking Forward. A quarter century of social change. University of New South Wales.

Zubrick, S. The Western Australian aboriginal Child Health Survey: Are there any policy implications? 20-22 September 2005. Imagining Childhood, children, culture & Community. Charles Darwin University, Alice Springs.

Zubrick, S. An epidemiological study of late talking 24 month old children: Prevalence and predictors. 5-8 July 2005. AHDA Conference, Perth.

Zubrick, S. Growing up in Australia: The Longitudinal Study of Australian Children. 5-6 July 2005. Australasian Human Development Conference, Perth.

Zubrick, S. Overview of measurement in Growing Up in Australia, 5 July 2005 Australasian Human Development Conference, Perth.



# Division of Virology

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, David Williams (Curtin University), John Mackenzie (Curtin University), Nadia Urosevic (Curtin University)

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 affect 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 of 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), David Evans (Glasgow University, Scotland), Steven Oberste (CDC, Atlanta, USA), Mary Jane Cardoso (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), Harri Kartini (BioFarma, Bandung, 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 enterovirus 71 (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 (ICRG) 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. 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. The HCMC group has since commenced EV71 surveillance in southern Vietnam and have undertaken a ground-breaking study of the molecular epidemiology of EV71 in this region. Several scientists from Indonesia (Jakarta, Bandung and Surabaya) will receive similar training in April 2006 and we anticipate EV71 surveillance to commence on the island of Java soon afterward.

#### Studies on the molecular genetics of enterovirus 71 encephalitis

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Peter McMinn, Chee Choy Kok, Lara Herrero, Beng Hooi Chua, Robert Hurrelbrink, Sharon Sanders, Darren Shafren (University of Newcastle), David Williams (Curtin University of Technology), Mary Jane Cardosa (UNIMAS, Sarawak, Malaysia)

As noted above, recent increases in the frequency and magnitude of 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 our research group has considerable expertise. The complete sequence of two local EV71 strains has been determined and full-length infectious cDNA clones constructed. We are now preparing virus chimeras in order to identify genome regions responsible for viral virulence and to develop a genetically defined, live attenuated vaccine strain. We have also developed the newborn mouse model of EV71 infection and are now using this model to undertake pathogenesis studies and to perform studies of vaccine efficacy.

We have also been undertaking research 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 is likely to be preferable to the newborn mouse model (see above) and will allow a detailed study of the pathogenesis of EV71 encephalitis, as

# Division of Virology

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. NHMRC Project Grants 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 (Hons) PhD, NHMRC Senior Research Fellow

Robert Hurrelbrink BA BSc (Hons) PhD, Wellcome Trust Senior Research Fellow (to June 2005)

Sharon Sanders BSc (Hons), NHMRC Graduate Research Assistant

### ■ Postgraduate Students

Beng Hooi Chua BS PhD candidate (UWA)

Lara Herrero BSc (Hons) PhD candidate (UWA)

Kristy Philippe BSc (Hons) PhD candidate (UWA)

Patchara Phuektes BVSc, MVSc PhD candidate (Murdoch)

## Awards

Kristy Philippe, Australian Postgraduate award, 2005-2008

Kristy Philippe, UWA Teaching Internship, 2006

Sharon Sanders, Australian Postgraduate Award, 2006-2009

## Visitors

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

Dr David Perera, Institute for Health and Community Medicine, UNIMAS, Sarawak, Malaysia

Dr David Williams, CRC for Emerging Infectious Diseases, Curtin University of Technology

## External committees

Peter McMinn. Member, W.A. State Arbovirus Control Committee, 1996-

Peter McMinn. Member, Health Department of WA Influenza Pandemic Planning Committee, 2004-

Peter McMinn. Chair, Princess Margaret Hospital Infection Control Committee, 1999-

Peter McMinn. Member, NHMRC Grant Review Panel 2B, 2004-

## Invited Presentations

Peter McMinn. Rebuilding health services in tsunami-stricken Aceh: re-establishment of public health laboratory services by the World Health Organization. Princess Margaret Hospital for Children Grand Round, Thursday 1st December.

Peter McMinn. Enterovirus 71 encephalitis in the Asia-Pacific Region. 6th Biennial convention of the ASEAN Neurological Association, Jakarta, Indonesia. Invited Plenary Speaker.

Lara Herrero. Receptor specificity of enterovirus 71 and other members of the human enterovirus A species. Proc. XIIIth International Congress of Virology, p. 75 (Session 80-V).

## Invited Postgraduate examiner

Peter McMinn. Ph.D. thesis for the Department of Medical Microbiology, Faculty of Medicine, the University of Malaya, Kuala Lumpur, Malaysia. Title: "Human Enterovirus 71 Phylogeny and Virulence Determinants." Author: Ms Chan Yoke Fun.



# Research collaborations - Phylogica

Phylogica is a biopharmaceutical company engaged in the discovery and development of novel biopharmaceuticals directed at proteins and their interactions. Phylogica was founded and incorporated in 2001, and is the first commercial spinout from the Institute to be publicly listed on the Australian Stock Exchange. Phylogica's proprietary technologies were developed as a result of close collaboration between the TICHR and The Fox Chase Cancer Center in Philadelphia ([www.fccc.edu](http://www.fccc.edu)), US. Both research centres are recognised for their excellence in medical research. Phylogica's technology platform has attracted over \$5 million in funding from international and national peer reviewed granting bodies such as the NIH, NHMRC, ARC and AusIndustry.

A core component of Phylogica's suite of technologies is the unique Phylomer® peptide library. This library consists of protein fragments, which have been sourced from an evolutionary diverse range of bacterial genomes. These bacteria have been collected from diverse and often harsh environments, in which their genomes have been subject to intense natural selection to evolve the most stable protein structures that facilitate survival of these organisms.

Consequently, the Phylomer® libraries are highly enriched for stable subdomains (15-50 amino acids long) of natural proteins, which we refer to as Phylomer® peptides, and which provide the source of high affinity peptide disruptors of protein interactions. Importantly, studies have shown that the Phylomer® libraries offer hit rates for targeted disruption of protein interactions that are 100-fold higher than alternative peptide-based screening

technologies. Further, the Phylomer® libraries, consist of an enormously diverse collection of stable peptide structures representing millions of potential drug candidates.

Phylogica has refined the process of drug discovery using the Phylomer® libraries by integrating this technology with high throughput screening platforms such as phage display and Phylogica's proprietary reverse yeast-two hybrid "Blocker Trap". These techniques facilitate rapid sampling of the Phylomer® libraries for the structures and shapes that are able to most efficiently disrupt specific protein interactions. Phylogica is currently applying its proprietary technologies for the development of drugs for the treatment of inflammatory diseases including, stroke, burns treatment, asthma and rheumatoid arthritis.

## Stroke Therapeutics: screening for Phylomer® disruptors of the Jun/Jun homodimer

V Cull, M Fear, D Shaw, D Dixon, N Milech, K Adcroft and PM Watt

Phylogica's lead project has been the research into peptide therapeutics for stroke. This project has been awarded funding via the AusIndustry, Biotechnology Innovation Fund (BIF) Program. This research is based on the evidence that the Jun-Jun homodimer is a critical protein complex involved in neuronal cell death in stroke. Disruption of this complex is likely to yield a potential therapy for reducing stroke-associated brain damage, which would have significant positive outcome for patients, and the cost of stroke treatment for the public health system.

A reverse-two hybrid approach, part of Phylogica's platform technology, has been used 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, and a subset of these peptides

were validated in a functional reporter assay using mammalian cells. Biophysical techniques are currently being used to study the nature of the interaction of these peptides with Jun. As part of a collaborative industry grant, the stability/ bioavailability and protective efficacy of these peptides in an *in vitro* stroke model are also being analysed. Peptides with demonstrated protective effect *in vitro* have been progressed through to a more sophisticated *in vivo* stroke model as the first pre-clinical animal trials for these potential therapeutics.

Importantly for Phylogica, a high percentage of the peptides effective in disrupting the Jun dimer are natural peptides. This strongly suggests that the Phylomer® peptide libraries indeed contain unique natural peptides that may constitute a novel source of potent and more effective peptide drugs.

#### Collaboration with The McComb Foundation to reduce damage caused by Burn Injury

M Fear, N Giles, S Rea, P Watt and F Wood

The long-term outcomes for burn injuries still remain very poor for people with moderate to severe burn injuries. Long-term functional disabilities and psychological problems prevent most burn sufferers from returning to the life they led prior to injury. Improving the outcome for patients with burn injuries has many advantages. It has the potential to decrease the long-term health costs associated with rehabilitation, which can take years, and to minimise the loss of quality of life and allow the individual to return to a normal productive life post-injury.

The treatment given at the time of injury is important, particularly with burn injuries, as even after the heat or chemical causing the burn has been removed the skin surrounding the injury continues to die. This results in the wound increasing in size, which makes it take longer to heal. If it were possible to prevent this continued damage at the time of injury, this would result in a smaller wound that can be healed quickly and with a better result.

This project is being carried out in collaboration with the McComb Foundation and involves using a Phylomer® discovered in a previous screen by

Phylogica to prevent apoptosis of keratinocytes. We have conducted preliminary experiments using a rodent model of full-thickness burn injury, and the initial data looks very promising. Not only does the wound appear to heal faster, a key component for reducing scarring, but also the re-vascularisation of tissue appears to be improved, making it less likely that large amounts of tissue would be lost. Currently we are continuing our studies in the rodent model, to extend the analysis of the effects and mechanism of action of the peptide, and will shortly be conducting experiments in more advanced animal models of burn injury.

#### Screening for Phylomer® therapeutics in oxidative stress conditions

N Milech, M Fear, K Adcroft, D Shaw and P Watt

Oxidative stress can cause damage to a number of cellular molecules such as proteins, DNA and lipids, and can ultimately lead to permanent damage and cell death. Oxidative stress is associated with an extremely wide range of diseases, including cardiovascular diseases, cancer, inflammatory diseases including arthritis, diabetes, and diseases of the central nervous system. While the particulars of each disease may be different, the cellular response to oxidative stress is a commonality.

The neural-protection studies from our stroke project have shown that some Phylomers® have anti-apoptotic potential, and there is a strong body of research that shows apoptotic cell death may be prevented by timely intervention with anti-apoptotic therapy. This project employed a phenotypic approach, using mammalian cells, to screen Phylogica's Phylomer® libraries for peptides that can protect cells against apoptosis induced by oxidative stress. Our objective is to identify anti-apoptotic Phylomers®, characterise their mode of action, and ultimately, study their therapeutic potential in a range of diseases.

#### Allergen Mimotopes

TK Heinrich, C.M. Hall, S. Winslow with L.A. Hazell B.J. Hales WR Thomas

Phage display technology using libraries

# Research collaborations - Phylogica

expressing random peptides has been used for identifying peptide that mimic epitopes (mimotopes). Essentially antibodies to the target antigen have been used to “pan” the libraries for phage expressing the peptide epitope by immunoabsorbent techniques. The mimotopes can be analogues of the sequence of the natural epitopes or can be peptides with an unrelated sequence that adapt an analogous structure. Mimotopes isolated in this way have the potential for a broad range of application in immunodiagnostic reagents and for vaccines or antigen-specific immunotherapy. While the ability to obtain mimotopes has been repeatedly demonstrated their utility has been limited mainly due to the low affinity interactions of mimotopes constituted of small random peptides. Allergen mimotopes are of interest because they would represent single epitopes and, by being monovalent and unable to cross link IgE on mast cells, be immunotherapeutic agents that could be used for allergy desensitisation in high dosage without side effects. The binding to antibodies additionally provides a model where the interaction of Phylomers® with ligands can be studied in a well defined system and in the case of allergen mimotopes the ability of the Phylomers® to immunise mice to produce anti-allergen antibodies provides a simple functional assay.

Antibodies to the major house dust mite (Der p 1 and Der p2) and cat (Fel d 1) allergens have been used as immunoabsorbents for panning phage display libraries. Two of five monoclonal antibodies tested enriched antibody-binding phage at high frequency (Der p 2 and Fel d 1) and one at low frequency (Der p 1). The Phylomers® isolated by the 10B2 anti-Der p 2 monoclonal antibody had a well-defined consensus sequence that resembled a sequence found in the original Der p 2 molecule. Fusion polypeptides were then produced with the 10B2 epitope (Der p 2 amino acids 69-82) and the glutathione-S-transferase (GST) of *Schistosoma japonica* and were used to immunise mice to induce anti-Der p 2 antibodies but the responses were variable. It was possible to improve epitope-specific immunisation with the use of a selected mimotopes. The mimotopes isolated with the Fel d 1 monoclonal antibody had a less stringent consensus sequence than that of the Der p 2 mimotope and

there was no sequence similarity with the natural allergen, showing a structural mimic. The mimotope studies have not resulted in the production of highly immunogenic Phylomer® mimotopes for allergens. They have however produced Phylomer® peptides that mimic antigen epitopes *in vitro* and have been a valuable system for optimising the phage display technology for future applications.

## Isolation and characterisation of peptide disruptors of Hepatitis C IRES initiated translation

M Fear, N Milech, K Adcroft, D Shaw and P Watt

Hepatitis C viral (HCV) infection is a significant health issue that affects millions of people world wide, and 40-60% of chronic liver disease is attributable to HCV infection. Unfortunately, current treatments are less than 50% effective and are costly. As a result, many patients do not receive the necessary therapies to fight the disease or treat the chronic condition. This project aims to investigate novel peptide therapies in HCV infection as alternative, directed therapeutics. After infection, HCV survives by using the cell machinery of the host cell to multiply, and then infect other cells. By targeting a virus-specific structure in the HCV genome, the Internal Ribosome Entry Site (IRES), we aimed to identify peptides that specifically disrupted viral translation, thereby inhibiting multiplication and spread of the virus through the body without affecting normal eukaryotic cellular processes.

In the process of this research, as well as isolating and characterising peptide disruptors of HCV IRES function, we have developed a screening platform that can now be used to target other viruses. This platform facilitates *ex vivo* genetic screening in mammalian cells for specific peptide inhibitors of viral IRES function, in this case inhibitors of HCV IRES, which we believe can offer alternatives to therapies currently on offer.

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

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

This project is applying 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  $\alpha$  and  $\alpha$  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  $\alpha$ -tubulin in *Cryptosporidium parvum*. These peptides are currently being tested to evaluate whether they disrupt  $\alpha$  and  $\beta$  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.

#### Development of next generation therapeutics for Rheumatoid Arthritis

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RM Hopkins, K Hoffman, T Heinrich, P Stumbles, C Hall, S Winslow, L Doan, R Kumar, W Thomas and P Watt, in collaboration with J Hamilton, Arthritis and Inflammation Research Unit, University of Melbourne, Victoria.

In October, 2005 Phylogica was awarded a \$4.5 million Commercial Ready grant from AusIndustry, to accelerate the development of its Phylomer® drug candidates for Rheumatoid Arthritis (RA). RA affects over 2.5% of the Australian population and costs the Australian economy over \$3 billion per year. Moreover, the market for anti-rheumatic drugs is forecast to expand at a compound annual growth rate of 24%, driven by technological advances, increased competition and significant unmet need for new therapeutic agents. This market is currently dominated by antibody-based therapies, against which Phylogica believes Phylomer® drugs can establish a strong competitive position.

Phylomer® peptides retain the same biological features as antibodies but also offer additional advantages including lower manufacturing costs, a simpler path to regulatory approval, and an ability to avoid the royalty stacks normally applied to antibody-based technologies. Hence, Phylomer® peptides represent a cost-effective alternative to the current biologics used to treat RA.

The specific aims of this proposal are to utilise the phage display screening platform to isolate Phylomer® peptides that inhibit the function of three key immunological targets, which play critical roles in the initiation of RA. Importantly, each of these candidates has been validated as a therapeutic target for RA, which reduces the risk associated with drug development. Furthermore, combinatorial blockade of their function has the potential to enhance the efficacy of treatment.

# Research collaborations - Phylogica

## Staff

■ Chief Scientific Officer, Phylogica

Paul Watt DPhil

Adjunct Associate Professor, The University of Western Australia

■ Research Staff

Katharine Adcroft BSc(Hons)

Vanessa Cull PhD

Darcelle Dixon PhD, Adjunct Lecturer UWA

Mark Fear PhD, Adjunct Lecturer UWA

Clinton Hall BSc(Hons)

Katrin Hoffmann PhD, Adjunct Lecturer UWA

Richard Hopkins PhD

Nadia Milech PhD, Adjunct Lecturer UWA

Daniel Shaw BSc(Hons)

Frank Sotzik PhD

Scott Winslow BSc(Hons)

■ Research Support

Stewart Cattach

## External Committees

■ Regional

Nadia Milech, Mark Fear and Darcelle Dixon. Australian Society for Medical Research (ASMR) WA, Fundraising and Professional Development Workshop Committee, 2005.

## Invited presentations

Paul Watt. Phylogica Ltd 7th World Congress on Inflammation, Melbourne, Australia, October 2005.

Mark Fear. Using Nature's Repertoire of Protein Scaffolds to Block Target Protein Complexes: A Novel Path to Specific Therapeutics? 6th Australian Peptide Conference, Hamilton Island Australia, October 2005.

Mark Fear. Functional Knockouts of Specific Protein Interactions. Human Proteome Organisation (HUPO) 4th Annual World Congress, Munich Germany, August 2005

Mark Fear. CSL Limited. Melbourne Australia, October 2005.

Paul Watt. Presenting Phylogica Ltd in session titled "Beyond Antibodies" AusBiotech 2005, Perth, Australia, November 2005.

## Acknowledgements

The Biotechnology Innovation Fund (BIF) grant funding from AusIndustry is gratefully acknowledged for its support of the stroke project.

The Commercial Ready grant funding from AusIndustry is gratefully acknowledged for its support of the rheumatoid arthritis project.



# Senior staff



## **Carol Bower**

*MBBS MSc PhD FAFPHM  
DLSHTM*

### *Head of Epidemiology*

Clinical Professor, University of Western Australia, Professor Bower has been a research scientist at the Institute since its 1990 opening. She established the internationally recognised Western Australian Birth Defects Registry, is a Fellow of the Australian Faculty of Public Health Medicine and holds a Principal Research Fellowship from the National Health and Medical Research Council.



## **Nick de Klerk**

*BSc MSc PhD*

### *Head of Biostatistics and Genetic Epidemiology*

Adjunct Professor, University of Western Australia, Professor de Klerk joined the Institute in 2000 after leading the Occupational Respiratory Epidemiology Group in the Department of Public Health at the University of Western Australia for 10 years. Before that he gained broad experience in biostatistics and epidemiology both in Western Australia and England.



## **John Finlay-Jones**

*BSc(Hons) PhD FAIBiol FASM  
Assistant Director*

Adjunct Professor, University of Western Australia, and Emeritus Professor, Flinders University of SA. A science graduate of the UWA, Professor Finlay-Jones spent 25 years at Flinders University, most recently as Head (Executive Dean) of the Faculty of Health Sciences, before joining the Institute in 2003. He has been President of the Australian Society for Medical Research (1990), the Australian Society for Microbiology (1996-1998) and the Australian Institute of Biology (1999-2001).



## **Robert Ginbey**

*BA BEd Grad Dip Public Sector Mgt MACE*

### *Head of Division of Admin and Corporate Services*

Mr Ginbey joined the Institute in 1995. He has taught history and economics in Western Australia and Papua New Guinea and more recently worked as a senior policy officer and senior manager of corporate services and strategic planning for both the commonwealth and state governments. He has coordinated two five yearly international reviews and the planning and opening of the Institute's current building.



## **Ursula Kees**

*Dip Phil II PhD*

### *Head of Division of Leukaemia and Cancer Research*

Adjunct Professor, University of Western Australia, Professor Kees has been a researcher at the Institute since its inception in 1990. She is interested in the molecular genetic mechanisms leading to cancer in children. In collaborative studies with the Oncology Total Care Unit at Princess Margaret Hospital for Children, she developed new methods for cancer diagnosis.



## **Deborah Lehmann**

*MBBS, MSc*

### *Member of Executive, Head of Infectious Disease Epidemiology Research*

Clinical Associate Professor, University of Western Australia, Professor Lehmann joined the Institute in 1998 after 18 years at the Papua New Guinea Institute of Medical Research where she headed a multidisciplinary Pneumonia Research Program. In November 2004, Deborah was appointed an Associate Professor at Curtin University of Technology. She provides expertise in infectious disease epidemiology and Indigenous health.



## **Bruce McHarrie**

*BCom CA*

### *Member of Executive, Chief Financial Officer*

Bruce McHarrie joined the Institute in 1999. He was previously an Assistant Director in the Bioscience Unit at Rothschild Asset Management in London and before that was with Coopers and Lybrand, also in London. Bruce has financial and executive management responsibilities as well as develops the Institute's commercialisation opportunities.



## **Peter McMinn**

*BMed Sc(Hons) MBBS PhD  
FRCPA FRCPATH DipRACOG*

### *Head of Division of Virology*

Peter McMinn is a virologist and Clinical Associate Professor, Discipline of Microbiology, School of Biomedical and Chemical Sciences, University of Western Australia. He spends half of his time in research at the Institute and half as a clinical virologist at Princess Margaret Hospital for Children.



**Prue Hart**

*BSc(Hons) MSc PhD  
Head of Inflammation  
Laboratory*

Principal Research Fellow, NHMRC and an Adjunct Associate Professor at the University of Western Australia. Professor Hart joined the Institute in July 2003 from Flinders University in Adelaide where she had been in the NHMRC Fellowship scheme since 1991. She has previously worked at University of Queensland (Royal Brisbane Hospital), Rigshospitalet in Copenhagen and the University of Melbourne (Royal Melbourne Hospital).



**Colleen Hayward**

*BEd BSc  
Manager, Kulunga  
Research Network*

Associate Professor, Curtin University, Colleen is a senior Noongar woman with family ties throughout the South-West of Western Australia. She has an extensive negotiation, advocacy, policy and management background in a range of government and non-government areas and was previously deputy Chief Executive Officer of the Aboriginal Legal Service of WA. Other experience covers areas including health, education, training, employment, housing.



**Pat Holt**

*PhD FRCPATH(UK) DSc FAA  
Member of Executive,  
Deputy Director, Head of  
Division of Cell Biology*

Professor Holt established the Division of Cell Biology in 1990. He is currently Senior Principal Research Fellow, NHMRC and holds a Professorship at the University of Western Australia. Previous appointments include Acting Director, Clinical Immunology Research Unit, Princess Margaret Hospital for Children; and Research Fellow, Institute of Environmental Hygiene, University of Gothenburg.



**Sven Silburn**

*BSc(Hons) MSc(Clin Psych)  
MAPS  
Director, Centre for  
Developmental Health*

Professor Silburn joined the Institute in 1991. Professor and Director, Centre for Developmental Health, Curtin University of Technology, Sven completed his clinical training in South Africa and worked in clinical child psychology for the Health Department of Western Australia. He Chairs the Ministerial Council for Suicide Prevention and is a principal investigator on the WA Aboriginal Child Health Survey.



**Peter Sly**

*MD FRACP DSc  
Member of Executive,  
Head of Division of Clinical  
Sciences*

Professor Sly established the Division of Clinical Sciences at the Institute in 1991. He is currently Director, Clinical Research and Education, Princess Margaret Hospital for Children; Professorial Fellow and Coordinator of Postgraduate Education, School of Paediatrics and Child Health, University of Western Australia; Senior Principal Research Fellow, NHMRC; Respiratory Physician, Princess Margaret Hospital for Children.



**Wayne Thomas**

*BSc Hons PhD  
Member of Executive,  
Head of Laboratory  
Sciences, Head of Division  
of Molecular Biotechnology*

Professor Thomas currently holds a Professorship at the University of Western Australia and is a Senior Principal Research Fellow, NHMRC. He has been division head since 1990. He has previously worked at the Medical Research Council, Clinical Research Centre London and at Walter and Eliza Institute for Medical Research. He is the chairman of the International Allergen Nomenclature Committee.



**Stephen Zubrick**

*MSc AM PhD  
Member of Executive,  
Head of Division of  
Population Sciences*

Professor Zubrick is a Senior Principal Research Fellow and holds a Professorship in the Institute and Curtin University's Centre for Developmental Health. He has worked in various mental health settings. He chairs the Consortium Advisory Group, National Longitudinal Study of Australian Children, sits on the Commonwealth Mental Health Promotion, Prevention and Early Intervention Working Party, and is a member of the Federal Government Australian Council for Children and Parenting.

# 2005 Publications

Alfonso HS, Fritschi L, de Klerk NH, Ambrosini G, Beilby J, Olsen N, Musk AW. Plasma concentrations of retinol, carotene, and vitamin E and mortality in subjects with asbestosis in a cohort exposed to crocidolite in Wittenoom, Western Australia. [Erratum appears *Journal of Occupational and Environmental Medicine* 2005;47:972]. *Journal of Occupational and Environmental Medicine* 2005;47:573-79.

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# 2005 Publications

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