TELETHON KIDS INSTITUTE

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ANNUAL REPORT 2013

SCIENTIFIC SUPPLEMENT

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The Telethon Kids Institute is affiliated with The University of Western Australia through the Centre for Child Health Research and has strong clinical research links to Princess Margaret Hospital for Children.

THE UNIVERSITY OF WESTERN AUSTRALIA

Government of **Western Australia**
Department of **Health**
Child and Adolescent Health Service

TELETHON KIDS INSTITUTE

Discover. Prevent. Cure.

KIDS are at the ♥ of everything we do

We've created a new kind of research institute – an institute where kids are at the heart of everything we do.

Our bold blueprint brings together community, researchers, practitioners, policy makers and funders, who share our vision to improve the health and wellbeing of children through excellence in research.

Over the past year, our organisation has undergone a significant transformation – reorganising our research and the structures that support it.

We're actively seeking broader collaborations and working closer with the community.

We're diversifying our funding sources with the aim of providing greater flexibility to pursue our research agenda.

And we've changed our name.

A new identity to match our new way of working. One that is bold and outgoing and embraces all who care about kids.

Together we will **Discover. Prevent. Cure.**

CELL BIOLOGY

Aetiology and pathogenesis of atopy and asthma in children

THE ROLE OF IGG ANTIBODIES IN CONTROLLING SYMPTOM SEVERITY IN CHILDREN WITH ALLERGIC RESPIRATORY DISEASE

Holt PG[a,b], Strickland DH[a], Hales B[a], Hollams EM[a] , Holt BJ[a], Belgrave D[c], Sly PD[b] and Custovic A[c]

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[c]University of Manchester, UK

Aeroallergen sensitization is common and risk for inflammatory airway disease increases with specific IgE levels. Paradoxically however, only a minority of sensitized children become symptomatic, suggesting that the potentially pathogenic sequelae of IgE triggering are usually efficiently controlled. It is known that a series of cell mediated mechanisms, particularly T-regulatory cells, contribute towards control of respiratory symptom severity. However research findings relating to occupational allergy and to immunotherapy suggest that an additional mechanism, involving allergen-specific IgG which is co-produced with IgE, may also play a role as a modulator of IgE-associated airways inflammation. However the potential role of aeroallergen specific IgG in modulating airways inflammation in atopic children has not been systematically evaluated.

We are addressing this issue employing a series of birth cohorts from Perth and UK via analysis of relationships between dust mite and cat-specific IgE and IgG and susceptibility to asthma, and corresponding Rye grass pollen-specific antibodies and susceptibility to rhinitis. Our preliminary findings suggest that the likelihood of airway symptoms amongst sensitized children increases with IgE titres, however risk is markedly attenuated in the presence of high levels of corresponding specific (total) IgG or IgG1 but not IgG4 i.e. when specific IgG1:IgE ratios are high. This apparent "IgE-sparing" effect in atopic children with high IgG1:IgE ratios is frequently mirrored by attenuation of skin prick test (SPT) responsiveness in the same subjects, suggesting that the IgG may block the access of allergen to IgE bound to IgE receptors on granulocytes. We are currently developing methods to advance these studies to encompass investigations on the role of IgG in regulating IgE-mediated basophil activation.

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

INVESTIGATING RELATIONSHIPS BETWEEN VITAMIN D STATUS AND ASTHMA AND ALLERGY DEVELOPMENT THROUGHOUT CHILDHOOD.

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[d]Queensland Children's Medical Research Institute, Brisbane, Australia.

Vitamin D has entered the spotlight in the search for preventive treatments against asthma and allergic disease due to its immune-modulating functions, shown in experimental models to include boosting protection against infection and promotion of immune tolerance. Vitamin D inadequacy is common, including in Australian children, but disparate findings from cohort studies have had a polarising effect on the scientific community regarding the wisdom of advocating vitamin D supplementation for protection against asthma and allergic disease. In this project we are testing the hypothesis that inadequate Vitamin D during early childhood promotes asthma development by increasing susceptibility to two major asthma risk factors: severe respiratory infection and allergic sensitisation. These risk factors have previously been shown to interact to elevate risk for asthma development by age 5 years in the Childhood Asthma Study (CAS) cohort, an intensively studied Perth cohort selected to be at high risk for asthma and allergic disease due to a positive parental history of allergy or asthma. The unique aspect of this cohort comes from the direct physician assessment of all respiratory infections that took place up to age 5years.

We used a highly specific method developed by Metabolomics Australia (University of Western Australia) to measure 25(OH)-vitamin D3 from cryobanked CAS plasma samples collected at regular intervals out to age 5 years. The concentrations of 25(OH)-vitamin D3 in cord blood were lower than we expected based on the existing literature, as less than 5% of the babies studied had what is currently considered "sufficient" vitamin D at birth (>75nM); quality control experiments confirmed that this was not due to problems recovering 25(OH)-vitamin D3 from cord blood. Between 6 months and 4 years of age 18%-28% of children were vitamin D deficient (<50 nM), but at ages 5 and 10 years deficiency was much less common (0.6% and 4% respectively).

Preliminary analyses have shown lower 25(OH)-vitamin D at age 6 months years predicted a higher number of severe lower respiratory infections up to age 2, and furthermore up to ages 3, 4, and 5 years, suggesting that a lack of vitamin D in early life may have a persistent detrimental effect on the ability of the immune system to fight off respiratory infections. More rigorous statistical analyses are underway.

This project is funded by Asthma Australia in conjunction with the National Health and Medical Research Council of Australia.

CHARACTERISATION OF NASOPHARYNGEAL MICROBIAL POPULATIONS IN CHILDREN AT HIGH RISK OF ASTHMA AND ALLERGY USING BACTERIAL METAGENOMICS

[a]Mok D, [b]Holt K, [c]Inouye M, [a]Hollams EM, [a]Holt BJ, [a]Kusel M, [d]Sly PD, [a]Holt PG

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[d]Queensland Children's Medical Research Institute, Queensland, Australia.

Recent data have shown that normal human lungs consist of a rich and phylogenetically diverse population of microbial communities. Moreover, colonization of specific bacteria in the nasopharynx of neonates has been implicated as a risk factor for the development of asthma early in life. We are conducting a metagenomic assessment of the upper and lower respiratory tract for bacterial populations using post-nasal aspirate and swab samples, obtained from individuals recruited in the Perth-based Childhood Asthma Study (CAS) birth cohort. This cohort is comprised of children at high-risk for asthma and atopy due to parental history of allergy. A total of 3379 samples have been extracted from cryobanked material, spanning age groups 3-6 months, 1, 2, 3, 4 and 5 years of age, taken either when the child was well and showing no respiratory symptoms for at least 4 weeks, or at the time of an acute respiratory illness. We are using the MiSeq (Illumina) platform to study the bacterial sequences, which produced highly comparable yet superior quality of reads compared to the platform previously used in our studies, the 454 FLX Titanium (Roche). The majority of samples have been processed and fully sequenced, and analysis of bacterial populations is ongoing by our collaborators at the University of Melbourne. Once we have accumulated these data across the age groups, we will proceed to identification of relationships between the composition and dynamics of the respiratory microbiome and the expression of transient and persistent airway symptoms in the children. These analyses will employ complex systems biology techniques aimed at the integration of the full range of clinical, immunological and microbiological data we have accumulated on the CAS cohort subjects into a systems level causal pathway describing the early stages of asthma pathogenesis.

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

ROLE OF IRF7 GENE NETWORKS IN ASTHMA EXACERBATIONS

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Human rhinovirus (HRV) infections are a major trigger for asthma exacerbations and are a frequent cause of hospitalization among children. Very few treatment options exist for asthma exacerbations, and progress towards the development of new treatments has been limited because the underlying disease mechanisms are poorly understood. We previously utilized a systems biology approach to characterize the gene networks that underpin the pathogenesis of asthma exacerbations in children. Our findings demonstrated that a gene called IRF7 was a master regulator of these networks. However, the data were based on a computational analysis and do not constitute direct proof. The objective of this ongoing project is to perform detailed mechanistic studies to dissect the role of IRF7 gene networks in asthma. The approach entails using siRNA to knockdown IRF7 in primary human airway epithelial infected *ex vivo* with rhinovirus. In parallel, systems biology studies will be performed in IRF7 knockout mice infected with virus. Finally, computational methods will be employed to identify drugs that modulate IRF7 gene networks, and these drugs will be tested in experimental models to determine if they can modulate virus-induced inflammatory responses.

This research is supported by a Medical Research Fellowship from the Brightspark Foundation and McCusker Charitable Foundation.

GENE NETWORK PATTERNS IN SPUTUM UNDERLYING ASTHMA-RELATED TRAITS

Jones A, White E, Hollams EM, Holt PG, Hall GL, Bosco A

Telethon Institute for Child Health Research, The University of Western Australia, Perth Australia

Asthma is a complex and heterogeneous inflammatory disease comprising multiple subphenotypes which are likely to be driven by distinct pathogenic mechanisms. Accumulating evidence suggests that new treatments currently in development for asthma are most effective when they are administered to patients who are selected on the basis of their specific disease subphenotype (stratified medicine). New methods are therefore urgently needed to profile molecular subphenotypes of asthma and identity the underlying causal pathways. We have previously shown that the induced sputum technique is a powerful and noninvasive method for sampling lower airway inflammatory cells for systems biology studies. The aim of this study is to use the induced sputum technique together with cutting-edge molecular profiling technologies and computational tools to identify the causal pathways that underpin asthma and related traits. The samples are being collected as part of the 23 year follow-up of the RAINE birth cohort.

This project is supported by funding from the Asthma Foundation of WA and the National Health and Medical Research Council of Australia.

IDENTIFICATION OF ALLERGEN-DRIVEN T CELL MEMORY GENE NETWORKS DURING EXPERIMENTAL ALLERGIC RHINITIS IN HUMANS

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The incidence of allergic diseases has reached epidemic proportions over the last few decades in the industrialized world. Detailed molecular studies of memory T cell responses in disease-relevant tissues in humans in vivo will be essential to understand the pathogenesis of allergic diseases. The objective of this study is to develop new methods to isolate highly purified CD4 T cells from allergen challenge sites

in humans for systems biology studies. Patients with allergic rhinitis are recruited out of season and challenged with allergen in the nasal cavity for seven days. Biopsies are obtained from the nasal mucosa before and after the allergen challenge. The biopsies are enzymatically digested into single cell suspensions and sorted into CD4 T cells and antigen presenting cells. Molecular profiling technologies are then employed to measure gene expression levels. The data showed that CD4 T cells isolated from allergen challenge sites are characterized by upregulation of Th2- and FoxP3-associated gene expression signatures. We are now conducting a follow-up study to repeat the experiments at multiple time points in a larger number of patients.

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

GENOMIC RESPONSES DURING ACUTE HUMAN ANAPHYLAXIS ARE CHARACTERIZED BY UPREGULATION OF INNATE INFLAMMATORY GENE NETWORKS

[b]Stone S, [a]Bosco A, [a]Jones A, [b]Cotterell V, [b]van Eeden P, [b]Arendts G, [b]Fatovich DM, [a]Holt PG, [b]Brown S.

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The pathogenesis of anaphylaxis in humans involves the systemic spread of immune activation and mediator release. Anaphylaxis in adults represents an extreme example of the inflammatory responses which drive the early phase of severe atopic asthma exacerbations in children, and we are studying this syndrome in adults to gain additional insight into the range of genes involved. The aim of this study is to investigate genomic responses during acute anaphylaxis in peripheral blood leukocytes. Peripheral blood samples are being collected from patients presenting to the Emergency Department with acute anaphylaxis and from healthy controls. Gene expression patterns are profiled on microarrays, differentially expressed genes are identified, and network analysis is employed to characterize the underlying mechanisms. The data show that innate inflammatory gene modules are upregulated in patients during acute anaphylaxis in comparison to healthy controls. Notably, these modules contain multiple hub genes, which are known to play a central role in the regulation of innate inflammatory responses. Bioinformatics analyses show that the data are enriched for TNF activation signatures. Our findings indicate a central role for innate immune pathways in the pathogenesis of human anaphylaxis, and the hub genes identified in this study represent logical candidates for follow-up mechanistic studies.

This project is supported by a grant from the US Food Allergy and Anaphylaxis Network.

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Aetiology and pathogenesis of asthma: Animal Model Studies

DEFECTIVE AEROALLERGEN SURVEILLANCE BY AIRWAY MUCOSAL DENDRITIC CELLS AS A DETERMINANT OF RISK FOR PERSISTENT AIRWAYS HYPER-RESPONSIVENESS IN EXPERIMENTAL ASTHMA

[a]Strickland DH, [a]Thomas JA, [a]Mok D, [b]Blank F, [a]McKenna KL, [a]Larcombe AN, [a]Sly PD, [a]Holt PG

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Atopic asthma contributes significantly to the overall community disease burden. Prospective cohort studies from our group have demonstrated that a major risk factor associated with the development of atopic asthma is sensitization to aeroallergens during early life years. While sensitization to aeroallergens *per se* is now extremely common and occurs in at least half of the Australian population, less than 25% of at-risk subjects progress to develop clinically relevant airways symptoms. This study aims to map the cellular immune mechanisms that underlie expression of clinically relevant persistent forms of allergic asthma. To achieve this, we have developed an experimental model system featuring rat strains at the two extremes of the spectrum of susceptibility to allergic airways disease: 1) high-IgE-responder (HR) BN rats (analogous to symptomatic human atopic asthmatics) in which sensitization with aeroallergen leads to high-level Th2-responses and subsequent aerosol challenge triggers rapid onset of severe and persistent airways inflammation and airways hyperresponsiveness (AHR), versus 2) low-IgE-responder (LR) PVG rats (analogous to the majority of aeroallergen-sensitized atopics) which are by comparison, refractory to aerosol challenge. In dissecting the cellular responses in the two rat strains we have identified that high susceptibility to aeroallergen-induced persistent airways disease in HR animals is a direct result of a specific deficit in the capacity to generate mucosal-homing Treg cells in airway draining lymph nodes (ADLN). The two key findings from our study are (i) the deficit in Treg induction in HR animals is linked to reduced capacity of their resident airway mucosal dendritic cells (AMDC) for in situ antigen uptake, and (ii) this defect in AMDC function is a direct result of signals from the local airway mucosal tissue microenvironment. We have demonstrated that this deficit can be therapeutically manipulated via intranasal transfer of *in vitro* aeroallergen-loaded AMDC from naïve animals into AHR-susceptible animals during prolonged aerosol challenge, which markedly boosts subsequent accumulation of iTregs in the airway mucosa and rapidly resolves their chronic AHR. This suggests that compromised antigen surveillance by AMDC results in defective functional programming of iTreg, which may be causally related to AHR susceptibility. Our future studies will characterize the tissue-specific immunomodulatory mechanism that determines antigen uptake capacity in HR rats in more detail, in the expectation that this knowledge will point to new targets for design of asthma treatment and prevention therapies.

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

RESPIRATORY VIRAL INFECTIONS AS TRIGGERS OF ACUTE SEVERE ASTHMA EXACERBATIONS IN ATOPICS: MECHANISTIC STUDIES IN AN EXPERIMENTAL MODEL

Strickland DH, Fear V, Thomas JA, PG Holt

Telethon Institute for Child Health Research, The University of Western Australia, Perth, Australia

There is strong epidemiological evidence implicating sensitization to aeroallergens as a potent asthma risk factor in children and young adults, and several large studies including our own have shown that the vast majority of young asthmatics are atopic. However, of all the individuals sensitized to aeroallergens, only a minority (<25%) progress to develop clinical symptoms of allergic airways disease, suggesting that additional cofactors are required to drive disease pathogenesis. The role of respiratory viral infections, in particular Rhinovirus (RV), in the allergic asthmatic disease process is currently one of the most active areas in asthma research, and represents a prime candidate for such a cofactor role in atopic asthma. It has been proposed that respiratory viral infections can operate in susceptible subjects independently of atopy and/or can apparently interact synergistically with the effects of atopy to maximise asthma risk. Additionally, there are claims of "reverse causality" i.e. that the atopic state may itself predispose to viral infections in the airways and that this may be sufficient to explain the association. Our own recent findings suggest that the connection between atopy and infection in this context may be more intimate. This study was designed to investigate the effects of respiratory viral infection in an established rat model of allergic asthma that mimics essential characteristics of the human disease. We have established a model for RV infection of rat strains expressing high (HR) versus low (LR) IgE responder phenotype, to best compliment the findings in humans that have shown strong associations between RV infection and acute asthma exacerbation in children. We have documented the inflammatory response to viral infection over a time course in naïve male and female HR and LR rat strains, including determination of viral titre, airways inflammatory responses, cytokine production and cellular immunology profiles of T cell and DC subsets. In addition, we have also exposed sensitized animals to viral infection, and following aerosol exposure to the sensitizing allergen at different times post initial viral inoculation we are investigating how allergic responses interplay with existing viral infection to influence local Th2 (allergic) immune responses to aeroallergen challenge in the airway mucosa.

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

LONG-TERM DERANGEMENT OF ANTIGEN PRESENTING CELL POPULATIONS IN THE RESPIRATORY TRACT FOLLOWING INFLUENZA A INFECTION

Stumbles PA, Smith M, Bozanich E, Fear V, Wikstrom M, Thomas J, Napoli S, Zosky GR, Larcombe AN, Sly PD, Berry C, von Garnier C, Holt PG and Strickland DH.

Telethon Institute for Child Health Research, The University of Western Australia, Perth, Australia

The maintenance of immunological homeostasis in the respiratory tract (RT) is important for normal function of the respiratory tissues, and the inhalation of environmental antigens continually challenges this system. The respiratory immune system must constantly screen antigens contained within inhaled air for their potential danger to the host and rapidly neutralize the threat, and alternatively must effectively ignore antigens if harmless. A balanced network of antigen presenting cells (APC) capable of regulating tolerance or immunity as required play an important role in this process. Via its potent inflammatory and cytotoxic activities, Influenza virus poses a serious threat to immunological homeostasis in the RT. Disruption to the balance of immunity in the RT can occur over a prolonged time frame following infection, potentially increasing the risk of allergic sensitization or decreasing resistance to secondary infections. In this project, we have used an experimental mouse model of H1N1 Influenza Type A Virus (IAV) infection to examine the dynamics and activation states of APC in airway mucosal (AM) and parenchymal lung (PL) tissue of the RT during and following a time course post IAV infection. In adult mice, we found marked differences in the selective depletion and reconstitution of dendritic cells (DC) subsets in the AM and PL environments. The response in AM DC was generally more acute and resolved by day 7 after infection, versus a more delayed response but with persistent depletion of PL DC lasting for up to 3 weeks following infection. Tissue-resident PL macrophages populations were also found to be significantly altered well after viral clearance, while these cells were depleted, those remaining were in a persistent state of activation. These studies were also performed in juvenile mice, and demonstrated persistent changes in PL DC and macrophages for up to 5 weeks following IAV infection. These data demonstrate that IAV has differential effects on APC populations in compartments of the RT, leading to long-term derangement in the numbers and activation states of these cells, that may disrupt the fine balance of immunological protection in this environment.

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

ROLE OF CD103 IN THE REGULATION OF IMMUNITY TO INHALED ALLERGENS

Fear V, Wikstrom M, Lai SP, Zosky GR, Stumbles P, Strickland DH

Telethon Institute for Child Health Research, The University of Western Australia, Perth Australia

CD103 is the α chain of integrin αEβ7, an adhesion molecule that mediates cell binding to epithelial cells via E-cadherin. This molecule is expressed by subsets of dendritic cells and T cells, and is important in T cell homing to epithelial barriers and marks a subset of dendritic cells that can mediate tolerogenic T cell responses to environmental allergens. In these studies we are examining the role of CD103 in the development of allergic asthma using mouse models of sensitization followed by inhaled-allergen challenge to induce allergic airways disease. CD103 knock-out ($CD103^{-/-}$) mice developed a range of hallmark features

of atopy and allergy, including OVA-specific IgE and elevated eosinophils in bronchoalveolar washings, although these were markedly elevated compared to sensitized and challenged wild type mice. Inhaled allergen capture and trafficking by dendritic cell subsets in the airways of CD103$^{-/-}$ mice was also altered, as well the generation and trafficking to the lungs of allergen-induced effector, memory and regulatory T cell subsets when compared to wild-type mice, with preliminary studies also suggesting that CD103$^{-/-}$ mice show modified lung physiological responses to methacholine following allergen challenge. These data suggest a pivotal role for CD103 in the early stages of systemic allergic sensitization and generation of allergen-specific IgE, as well as at later stages in the initiation and regulation of the local lung immune responses to allergen rechallenge.

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

MECHANISMS OF IGE SENSITIZATION

Strickland DH, Mincham KT, Thomas JA, Stumbles P, Holt PG.

Telethon Institute for Child Health Research, The University of Western Australia, Perth Australia

A key risk factor that has been identified in association with the rising prevalence of allergic asthma is an increase in atopic (IgE mediated) sensitization to aeroallergens. To date, there has been limited progress in dissecting the nature of the antecedent immunological mechanisms that underlie generation of mucosal IgE sensitization, as opposed to the normal response of protective tolerance to aeroallergens. The induction of "mucosal tolerance" to aeroallergen, initially described and characterised in animal model studies from our laboratory, represents one of the established paradigms in lung immunology. Selective attenuation of Th2 skewed immunity, particularly production of IgE, can be attained by repeated exposure via the respiratory route. This was associated with induction of a phenotypically heterogeneous population of T cells with "regulatory" activity. Of note, induction of tolerance in animals that are hyper-susceptibile to allergic disease and develop high IgE responses (high responder; HR) required log fold higher levels of exposure to OVA than their low-responder (LR) counterparts or dust mite allergen. No satisfactory explanation exists to explain this profound difference in efficiency of mucosal tolerance mechanisms. This study derives from recent novel and counterintuitive epidemiological findings suggesting that risk for IgE sensitization to inhalant allergens may be inversely related to allergen exposure levels. Our core hypothesis is that variations in the functional capacity of respiratory immune cell surveillance mechanisms results in a spectrum of susceptibility to development of protective IgE tolerance to aeroallergens, and our HR/LR rat model provides unique opportunities to systematically test that hypothesis. Our preliminary studies align well with our core hypotheses and suggest that in LR rats, intranasal exposure to daily high dose antigen results in earlier development of IgE tolerance and that this is associated with earlier increased induction of iTreg in the DLN.

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

TARGETING THE MUCOSAL IMMUNE SYSTEM IN A MOUSE MODEL TO PREVENT PREGNANCY COMPLICATIONS

Scott NM, Mincham KT, Prescott SL, Robertson SA, Holt PG, Strickland DH

Telethon Institute for Child Health Research, The University of Western Australia, Perth Australia

Maternal infection has been associated with pregnancy complications including increased mortality and morbidity for mother and fetus. Bacterial and viral infections can induce preterm delivery and are associated with low birth weight, which can have detrimental impact on child growth and development during early life and represent significant risk factors for development of non-communicable diseases in later life. Preterm birth is the single most important health care issue in fetal-maternal medicine, with a high prevalence in Australia and other developed countries. Safe effective treatments that can be used to protect against infection-induced complications would provide exciting new opportunities for improving pregnancy health for all women. Rodent models are well validated to study mechanisms underlying infection induced pregnancy complications. Lipopolysaccharide (LPS), the major pathogenic component of gram-negative bacteria can induce preterm delivery, growth retardation, embryonic resorption and reduced fetal survival, when delivered to pregnant mice. In this study we are investigating the therapeutic potential of an immune modulating agent (OM85BV – a bacterial extract) delivered via the gut mucosa, to protect against complications induced by LPS administered during late gestation. Our preliminary results have shown that treatment of pregnant mice with OM85BV for one week prior to LPS exposure provides a level of protection against the LPS induced changes to fetal growth and survival, potentially via modulation of immune cell populations in the intrauterine tissues. This pre-clinical study suggests that treatment with OM85BV during pregnancy may represent a novel, safe effective treatment strategy to protect against bacterial infection-induced complications during pregnancy.

This project is funded by the National Health and Medical Research Council of Australia and OM Pharma (Geneva).

MATERNAL ALLERGIC ASTHMA: PREGNANCY COMPLICATIONS INDUCED IN MOTHER AND FETUS

Mincham KT, Scott NM, Prescott SL, Robertson SA, Holt PG, Strickland DH

Telethon Institute for Child Health Research, The University of Western Australia, Perth Australia

Maternal asthma is known to affect 12% of Australian pregnancies. It is now understood that sporadic asthma exacerbations during pregnancy pose a significant threat to the health of the fetus, exemplified through preterm delivery and low birth weight. Of significance, preterm birth and low birth weight have been identified as potential risk factors for the onset of non-communicable diseases in adulthood, including coronary disease, hypertension and diabetes. Preterm birth has also been associated with the development of wheezing disorders during childhood. Further, maternal asthma during pregnancy has been linked to an

increased likelihood of the neonate developing allergic asthma at a later stage. In addition to the threat to fetal health, it is now clear that during pregnancy, asthmatic women are themselves at increased risk of worsening asthmatic disease symptoms. This study will use our well-established mouse models of allergic asthma as a basis to develop an experimental model of allergic asthma during pregnancy. This tool will be used to i) document health of mother and fetus following allergic asthma exacerbations during the gestational period, including gestational length, birth weight, asthmatic responses of the mother and ii) determine the impact of maternal asthma on the development of the offspring and risk for developing allergic asthma, and iii) determine underlying cellular immune mechanisms that play a role in disease processes. Additionally we will investigate the therapeutic potential of an immune modulating agent (OM85BV – a bacterial extract) delivered via the gut mucosa, to protect against pregnancy complications in asthmatic women. This pre-clinical proof-of-concept study is aimed at providing the rationale for future translational studies in humans, where the proposed target group for treatment in the first instance is atopic mothers whose offspring are known to be at high risk of asthma.

This project is funded by the National Health and Medical Research Council of Australia and OM Pharma (Geneva).

DIFFERENTIAL ACTIVITY OF TYPE I INTERFERONS ON AIRWAYS RESPONSE TO ALLERGEN.

Fear VS, Holt PG, Strickland DH.

Telethon Institute for Child Health Research, The University of Western Australia, Perth Australia

Asthma is a significant and increasing health burden, impacting on personal quality of life, lost work productivity and the health service. Recent studies implicate early life respiratory viral infection and concomitant IgE sensitisation to allergen as strong risk factors in the development of atopic asthma. One hypothesis is that signals elicited in response to respiratory viral infection cross stimulate responses to allergen, leading to sensitization and subsequent allergic asthmatic responses. The early innate immune response to respiratory viral infection is high level Type I IFN production from dendritic cells and airway epithelial cells. Therefore, this family of cytokines may potentially play a key role in the viral induction of inappropriate responses to airway allergen, which contribute to the development of asthma. Two key cell types involved in the development, progression and resolution of allergic asthma exacerbations include airway mucosal DCs and T regulatory cells. This project examines the effect of IFNα2 and IFNβ intranasal delivery on airway dendritic cells, T cells and T regulatory cells. We demonstrate the influence of IFNα2 and IFNβ intranasal delivery on the development of sensitization and/or tolerance to allergen.

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

Staff and Students

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Ms Marina Stubbs – Administration Officer

External Committees

Patrick Holt: NIH Expert Committee on Immunotherapy.

Patrick Holt: NIH Expert Committee: Development of strategies for asthma prevention

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

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

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

Patrick Holt: Scientific Advisory Committee, Pediatric Research Centre, University of Hanover

Patrick Holt: NIH Program Scientific Advisory Committee, MAAP Project, Henry Ford Hospital, Detroit

Patrick Holt: Scientific Consultant; Christine-Kühne Center for Allergy Research and Education, Munich

Invited Presentations

INTERNATIONAL

Prof Patrick Holt: Symposium Speaker: Early signs of immune deviation towards allergy - American Academy of Allergy, Asthma and Immunology Congress, San Antonia, 2013.

Prof Patrick Holt: Keynote Address: Emerging opportunities for asthma prevention; Opening of Pediatric Research Centre, University of Hanover, 2013.

Prof Patrick Holt: Symposium Speaker: Immune responses against respiratory infections in children – ELAIR Congress, Mexico City, 2013.

Prof Patrick Holt: Symposium Speaker: The inflammatory cycle in asthma pathogenesis – Global Allergy Forum, Davos, 2013.

Prof Patrick Holt: Workshop Presenter: The respiratory bacteriome and asthma risk - Global Allergy Forum, Davos, 2013.

Prof Patrick Holt: ALK Abello, Copenhagen, 2013; Biomarkers of responsiveness to immunotherapy.

Dr Anthony Bosco: Plenary lecture: Joint Congress of the Malaysian Society of Allergy and Immunology (MSAI) and the Allergy and Clinical Immunology Society Singapore (ACIS), Kuala Lumpur. Maturation of immune function in early life.

Dr Anthony Bosco: Plenary lecture: Joint Congress of the Malaysian Society of Allergy and Immunology (MSAI) and the Allergy and Clinical Immunology Society Singapore (ACIS), Kuala Lumpur: Viruses and atopy.

NATIONAL

Dr Deborah Strickland: DC Downunder symposium, Sydney, oral presentation

Dr VS Fear: Immunomodulatory effects of type I IFN in the development of sensitisation to allergen. Australian Society for Immunology, 42nd Annual Scientific Meeting Perth Immunology Group, seminar.

Dr Vanessa Fear: Type I IFN subtypes show differential efficacy in the treatment of melanoma. 8th State Cancer Conference, Cancer Council WA, seminar.

Prof Patrick Holt: Aetiology and pathogenesis of asthma. Queensland Childrens Medical Research Institute, Brisbane.

LOCAL

Dr Deborah Strickland: ASMR, Session Chair

Dr Anthony Bosco: Grand Round TICHR presentation. Princess Margaret Hospital. Development of a framework for Translational Systems Immunology.

Dr Anthony Bosco: University of Western Australia Workshop on Complex networks: a perspective for understanding real-world problems

Dr Anthony Bosco: Asthma Foundation of Western Australia: A new approach to elucidate asthma endotypes.

Dr Anthony Bosco: Plenary lecture: 24th Annual Scientific Meeting of the Australasian Society of Clinical Immunology and Allergy (ASCIA). Using network graph theory to understand allergy and asthma.

Dr Anthony Bosco: Lung Institute of WA (LIWA) Medical Research Seminar Series: Role of gene networks in asthma.

Dr Anthony Bosco: Rottnest Annual Scientific Respiratory Meeting. Using network graph theory to understand asthma.

ACTIVE collaborations

Fernando Martinez, Respiratory Sciences Center, University of Arizona, USA

James Gern, Clinical Science Centre, University Of Wisconsin Medical School, USA

Robert Lemanske, Division of Pediatric Allergy, Immunology and Rheumatology, Wisconsin University, USA

Adnan Custovic, University Hospital of South Manchester, UK

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Steffan Ahlstedt, Karolinska Institute, Sweden

Charles Hardy, Monash University, Melbourne, Australia

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John Upham, Director of Lung and Allergy Research Centre, School of Medicine, The University of Queensland.

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CANCER AND LEUKAEMIA RESEARCH

Overview

Cancers in children comprise many different diseases. More than half of them affect cells of the immune system and the central nervous system. In contrast, the most common types of cancer in adults are carcinomas and they begin in the cells that line the surface of the body and internal structures. Thus, the most common malignancy in children is leukaemia, followed by brain tumours. Despite marked improvements in the cure rates for paediatric cancers, leukaemias and brain tumours account for half of the deaths. In order to find better therapies for children with cancer, our Division at the Institute and the Oncology Total Care Unit at Princess Margaret Hospital (PMH) are both members of the largest study group into these diseases, the US-based Children's Oncology Group (COG). The major goal is to improve our understanding of paediatric cancers and leukaemia, and work towards curative therapy for patients.

The Division focuses on research into childhood leukaemia, brain tumours and a very rare disease in children, a form of carcinoma. 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 whole genome sequencing technologies and high-throughput drug screening. Our experimental model systems, including a panel of established leukaemia and cancer cell lines, are ideal tools for testing potential new drugs for the treatment of patients.

Leukaemia

HIGH LEVELS OF CONNECTIVE TISSUE GROWTH FACTOR CAN ACCELERATE DISEASE IN A MODEL OF ACUTE LYMPHOBLASTIC LEUKAEMIA

Investigators: JE Wells, M Howlett, HM Halse, J Ford, J Heng, LC Cheung and UR Kees in collaboration with CH Cole, Haematology-Oncology, Princess Margaret Hospital.

Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children. Despite major improvements in cure rates, a significant number of patients relapse and their prognosis remains dismal. ALL originates in the bone marrow and cell-cell interactions in this microenvironment can alter disease progression and treatment efficacy.

Connective tissue growth factor (*CTGF/CCN2*) is expressed at significantly higher levels in approximately 75% of pre-B ALL specimens compared to normal cells. *CTGF* is a secreted protein with functions in mesenchymal stem cell differentiation, fibrosis and cancer. Mechanisms of action include neo-vascularisation, migration, and proliferation. The role of *CTGF* in ALL is currently unknown. Addition of *CTGF* to two bone marrow stromal cell lines enhanced their proliferation rate while it had no effect on the proliferation of four pre-B ALL cell lines. Using lentiviral technology we modified a patient-derived pre-B ALL cell line, PER-371 to express and secrete high levels of *CTGF*, which did not alter their proliferation rate in vitro. However, when xenografted in NOD/SCID mice, high *CTGF*-expressing PER-371 cells showed accelerated leukaemic development. The median survival was 70 days, compared to 89 days (p=0.03) for mice injected with PER-371 control cells that express basal levels of *CTGF*. We determined whether high gene expression led to distinct cell homing in xenografted mice. Leukaemic cell infiltration was measured in haemopoietic organs of mouse cohorts at three time points during disease development. There were no significant differences in leukaemic cell infiltration early in disease, however, high *CTGF*-expressing PER-371 cells were significantly increased in the bone marrow approximately two weeks before full development of disease compared to control PER-371 xenografts (44% vs 8%; p=0.01). This suggests that high levels of *CTGF* in these cells does not influence homing, but confers a growth advantage within the bone marrow niche. Using lentiviral shRNA technology, we recently generated pre-B ALL cell lines with reduced levels of secreted *CTGF*, resulting in significantly reduced proliferation *in vitro* in two pre-B ALL cell lines. PER-371-shCTGF proliferation was reduced by 99% (p<0.005) and PER-377-shCTGF by 95% (p<0.005) compared to respective controls. *In vivo* studies using these cell lines are in progress and will determine if CTGF is an effective target for treatment of ALL patients.

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

HYPOMETHYLATION OF THE CTGF GENE LOCUS IS A COMMON FEATURE OF PAEDIATRIC PRE-B ACUTE LYMPHOBLASTIC LEUKAEMIA

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

Connective tissue growth factor (*CTFG*) is a matricellular protein aberrantly expressed in a high proportion (75%) of B-lineage acute lymphoblastic leukaemias (pre-B ALL) and is associated with poor outcome. We investigated the role of genetic and epigenetic factors leading to *CTGF* expression in paediatric pre-B ALL. Our findings reveal that methylation of the *CTGF* CpG island, rather than gene copy-number changes, translocations or mutations, correlate with expression of *CTGF* in pre-B ALL. The *CTGF* gene contains a dense 5' CpG island (CpGi) and methylation-specific PCR identified an inverse correlation between *CTGF* gene expression and methylation of the *CTGF* CpGi in pre-B ALL cell lines, and this finding was confirmed using bisulfite sequencing. Culture with 5-aza-2'-deoxycytidine and Trichostatin-A resulted in a significant increase in *CTGF* expression, confirming that global changes in DNA methylation and histone acetylation can influence *CTGF* transcription. Bisulfite sequencing revealed hypomethylation of the *CTGF* locus was a consistent feature of primary B-lineage ALL. By contrast T-ALL specimens, which do not express *CTGF*, were hypermethylated. Bone marrow derived $CD34^{pos}$ cells were found to be completely unmethylated at the *CTGF* locus. These findings provide the basis to examine gene-targeted approaches to achieve epigenetic reprogramming of *CTGF* expression in leukaemia.

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

THE ROLE OF CONNECTIVE TISSUE GROWTH FACTOR (CTGF) IN HAEMATOPOIESIS

Investigators: LC Cheung , M Howlett and UR Kees in collaboration with DH Strickland, Division of Cell Biology, and CH Cole, AK Charles, Princess Margaret Hospital, Perth and WS Alexander, Walter and Eliza Hall Institute of Medical Research, Melbourne, and KM Lyons, UCLA, Los Angeles, USA.

Connective tissue growth factor (*CTGF*) is a member of the CCN gene family, whose protein products have critical roles in bone formation, and in fibroblasts, chondrocytes and endothelial cells. Our previous studies showed that *CTGF* was highly upregulated in acute lymphoblastic leukaemia of pre-B type (pre-B ALL). *CTGF* also plays a role in osteoblast proliferation and differentiation, and these cells are known to control haematopoietic stem cells (HSCs) *via* production of factors essential for renewal and maturation. The balance of HSC self-renewal and differentiation is highly regulated by intrinsic factors together with cues from the surrounding microenvironment, including growth factors. Hence, we hypothesize that *CTGF* plays a role in haematopoiesis. We studied mice with targeted disruption of the *Ctgf* gene. Using multi-colour flow cytometric analyses, different lineage populations in various haematopoietic organs from $Ctgf^{-/-}$ and wild type (WT) mice were enumerated. Because $Ctgf^{-/-}$ mice die perinatally, the haematopoietic potential of cells from $Ctgf^{-/-}$ and WT fetal livers was compared using a chimera transplantation models. Furthermore, mRNA expression of *Ctgf* was examined in the bone marrow compartment.

While adult $Ctgf^{+/-}$ mice appeared to have normal haematopoiesis, $Ctgf^{-/-}$ newborn mice exhibited impaired haematopoiesis. Using chimeric transplantation models, we demonstrated that absence of *Ctgf* had an impact on B-cell development, in particular from pro-B to more mature stages, which was linked to a requirement for *Ctgf* in bone marrow stromal cells (BMSCs). Additionally, sorted BMSCs were found to have high *Ctgf* expression, and this was evident in newborn and adult mice. In contrast, *Ctgf* was barely detectable in unfractionated adult bone marrow cells and no *Ctgf* expression was detected in isolated B-cell subpopulations, indicating BMSCs are the major source of *Ctgf* in the bone marrow microenvironment. Using *in vitro* culture systems, **$Ctgf^{-/-}$** BMSCs led to impaired B-cell differentiation from pro-B to more mature B cells, further demonstrating *Ctgf* is required in BMSCs to maintain B-cell function. Lastly, *CTGF* potentiated B-cell proliferation and promoted pro-B to pre-B differentiation in the presence of IL-7. Further investigations are in progress to elucidate the exact mechanism.

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

PHARMACOGENOMIC MODELLING IN VITRO REVEALS THE CLINICAL IMPORTANCE OF 6-MERCAPTOPURINE THERAPY FOR OUTCOME IN PAEDIATRIC LEUKAEMIA

Investigators: AH Beesley, A Samuels, J Ford and UR Kees in collaboration with D Anderson and MJ Firth, Division of Biostatistics and Genetic Epidemiology.

Children with acute lymphoblastic leukaemia (ALL) are treated with complex chemotherapy regimens of up to ten different drugs according to risk stratification at diagnosis. Around 80% of patients achieve continuous complete remission with early response to drug therapy being one of the strongest predictors of outcome. However, patients relapsing with T-cell ALL (T-ALL) face a dismal outcome. The aim of this study was to identify new markers of drug-resistance and clinical response in T-ALL. We measured gene expression and drug sensitivity in 15 paediatric T-ALL cell lines to find signatures predictive of resistance to ten drugs used in therapy. These were used to generate a model for outcome prediction in patient cohorts using microarray data from diagnosis specimens. In three independent T-ALL cohorts the ten-drug model was able to accurately identify patient outcome, indicating that the in vitro derived drug-gene profiles were clinically relevant. Importantly, predictions of outcome within each cohort were linked to distinct drugs, suggesting that different mechanisms contribute to relapse. Sulfite oxidase (*SUOX*) expression and the drug-transporter *ABCC1* (MRP1) were linked to thiopurine sensitivity, suggesting novel pathways for targeting resistance. This study advances our understanding of drug resistance in T-ALL and provides new markers for patient stratification. The results suggest potential benefit from the earlier use of 6-mercaptopurine in T-ALL therapy or the development of adjuvants that may sensitize blasts to this drug. The methodology developed in this study could be applied to other cancers to achieve patient stratification at the time of diagnosis.

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

WHOLE EXOME SEQUENCE AND GENE-EXPRESSION ANALYSES OF AN IN VITRO MODEL OF T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA DRUG RESISTANCE

Investigators: MN Cruickshank, J Ford, AM Gout, AH Beesley and UR Kees.

Detection of chromosomal abnormalities in leukaemia can provide prognostic markers used to guide treatment. However, genetic alterations predicting response to chemotherapy in paediatric T-cell acute lymphoblastic leukaemia (T-ALL) are poorly defined. We are investigating mechanisms of T-ALL resistance to flavopiridol (FP), an isoflavone compound with cyclin-dependent kinase inhibitor activity.

We generated FP-resistant T-ALL clones by long-term drug exposure of PER-255 cells followed by limiting dilution. Exome-sequencing was performed on FP-resistant clones and parental T-ALL cells. Burrows-Wheeler Aligner (BWA) was used for alignment (hg19, GRCh37), PCR duplicates were removed with SAMTools, GATK functions were used for base quality recalibration and realignment around microindels. Unified Genotyper was used to call single nucleotide variants (SNVs). Exonic, non-synonymous SNVs were filtered to identify variants with at least five identical non-reference genotypes from at least 20 total reads. Gene expression profiling was performed using the Affymetrix® Human Gene ST Array on untreated PER-255 cells and 8 hours after FP treatment with five biological replicates.

FP is cytotoxic in PER-255 cells with 50% inhibitory concentration (IC50) observed of 37.9

nM. The resistant clones ranged in IC50 from 72.1-82.8 nM flavopiridol (n=4). Comparison of FP-resistant and parental exome data identified 378 SNVs among resistant clones that were undetectable in parental T-ALL cells (n=2). Of the common variants associated with FP-resistance, 40 were predicted to cause damaging mutations. These included six novel variants. A total of 212 predicted damaging variants in 181 unique genes were shared in two or more FP-resistant clones. Gene ontology analyses of shared variants suggested enrichment of genes involved in immune responses and drug metabolic processes. Differential expression analysis identified 143 differentially expressed genes following FP-treatment (adjusted $p<0.05$; Log2-fold change>1.5) enriched for genes encoding catalytic enzymes. Comparing exome-seq data and microarray data, we found two distinct UGT-family genes (UDP-glucuronosyltransferase enzyme encoding genes) associated with FP treatment. These genes are involved in isolflavone metabolism and may be involved in FP-response or drug-resistance.

We provide proof of principle for *in vitro* selection and exome-sequencing to identify sequence alterations associated with drug-resistance. Our results identified candidate genetic variants in T-ALL cells resistant to a CDK-inhibitor currently under trial to treat various cancers, including acute and chronic leukaemias and carcinoma. Further studies to explore if these variants arise in T-ALL or FP-treated patients who develop drug-resistance may reveal the clinical relevance of genetic alterations identified in this model system.

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

MODULATION OF ENERGY METABOLISM PATHWAYS ASSOCIATED WITH GLUCOCORTICOID RESISTANCE IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA (T-ALL)

Investigators: AL Samuels, J Heng, F Ong, AH Beesley and UR Kees in collaboration with KW Carter and RW Francis, Division of Biostatistics and Bioinformatics.

Leukaemia is the most common cause of cancer in children. Steady progress has pushed the cure rate in paediatric patients to >80% in some subtypes of the disease. The outlook, however, for patients with T-cell acute lymphoblastic leukaemia (T-ALL), particularly drug-resistant patients is dismal, with event free survival rates <15%. Current treatment regimens are harsh involving a combination of up to 10 different drugs, which are frequently associated with both long- and short-term side effects. But resistance to agents used in the initial phase of therapy, particularly steroids (glucocorticoids) is one of the strongest predictors of adverse outcome. Improving the outcome of these patients requires the identification of specific molecular mechanisms that drive resistance to therapy and the development of new strategies to target them.

Importantly, our research recently identified that glucocorticoid resistant leukaemia cells alter their glucose energy metabolism. We found that drug-resistance is associated with an increased glycolytic phenotype and protection from metabolic crisis in T-ALL. Using a unique panel of leukaemia cell lines we were able to overcome drug resistance by targeting these unique pathways (Samuels et al., 2014, British Journal of haematology). Collectively, our findings suggest that dual targeting of bioenergetic pathways in combination with glucocorticoids may offer a promising therapeutic strategy to overcome drug resistance in ALL. To further investigate how these metabolic pathways mediate drug resistance we have developed novel profiling approaches to identify the proteins and metabolites specifically deregulated in steroid resistant leukaemia. Metabolomic and proteomic analysis identified significant alterations in key bioenergetic pathways associated with drug resistance. The function of these proteins and pathways is currently being investigated to identify therapeutic approaches to target steroid resistance. These experiments aim to identify novel targeted proteins that can overcome glucocorticoid resistance, thereby addressing a critical unmet need in the clinical management of T-ALL.

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

TARGETING DRUG RESISTANCE IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

Investigators: AL Samuels, AH Beesley, F Ong and UR Kees in collaboration with B Yadav and R Lock, Leukaemia Biology, Children's Cancer Institute Australia for Medical Research, New South Wales.

Drug resistance continues to be a significant problem in childhood T-cell acute lymphoblastic leukaemia (T-ALL), yet few novel therapies have emerged over the last decades. To identify genes and pathways deregulated in drug resistance, as well as small molecule inhibitors that could synergise with current therapies, we have established and validated a powerful preclinical *in vivo* model of ALL induction therapy that allows for the investigation of mechanisms of resistance. Using a clinically relevant four-drug treatment regimen we have demonstrated that this model accurately recapitulates the *in vivo* development of drug resistance. This approach identified biological signatures associated with the development of resistance *in vivo* and determined, that patterns of resistance are different amongst tumors derived from individual patients. In two of the four leukemia lines tested, no drug resistance emerged after repeated drug treatment, and this correlates with the clinical course of the patients in question since these individuals remain in clinical remission. However, the two other leukemia lines developed drug resistant

phenotypes associated with distinct changes in gene expression, including, changes to lipid and carbohydrate metabolism, an observation that led us to focus on a number of agents that modulate these pathways as a proof-of-concept approach to overcome resistance in ALL.

We are currently extending this study to larger numbers of ALL xenografts to capture a greater diversity of relapsing profiles. The molecular alterations driving acquired drug resistance will provide important clues for the development of new therapeutic strategies for the treatment of T-ALL.

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

DRUG-INDUCED CHROMATIN STATE, CELL CYCLE ALTERATIONS AND HIGH-THROUGHPUT DRUG SCREENING IN MLL-REARRANGED INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA

Investigators: MN Cruickshank, J Ford, J Heng, and UR Kees, in collaboration with D Anderson, Division of Biostatistics and Bioinformatics, and CH Cole, Haematology-Oncology, Princess Margaret Hospital.

The survival rate of infants with acute lymphoblastic leukaemia (iALL) with a translocation at the MLL-locus (MLL-r) is only 30%. MLL encodes a histone methyltransferase (H3K4) that is part of the trithorax complex, an evolutionarily conserved developmental regulator of chromatin structure. We sought to identify novel therapeutics for MLL-r iALL by high-throughput drug screening of iALL cells. We explored the mechanisms of action of two effective drugs. Mechanisms of drug actions were examined by flow cytometry to measure cell cycle and chromatin state alterations at single-cell resolution after 24 h drug exposure. Cells were harvested, permeabilized and stained with antibodies against H3K27-acetylation and H3S10-phosphorylation. Both modifications were quantified simultaneously using dual colour flow cytometry. Cell cycle was assessed using propidium iodide (PI) staining.

Many of the currently used drugs did not cause cell death in iALL. Several compounds that were effective *in vitro* are not used in contemporary protocols. Many novel compounds identified as effective iALL drugs, such as Vorinostat, are known epigenetic modulators in various cancer types. We examined cell cycle and chromatin state following exposure of iALL cells to effective drugs, operating by distinct mechanisms: Vorinostat a histone deaceyltylase inhibitor (HDACi) and Vincristine (VCR) an alkaloid and microtubule inhibitor. We found opposite effects on cell cycle, such that Vincristine caused accumulation of cells at S- and G2/M phases; while Vorinostat caused accumulation of cells at G0-G1 phase. Intriguingly, Vorinostat treatment resulted in a bimodal population of cells with respect to histone H3K27-acetylation. Furthermore, Vorinostat altered the abundance and cell composition with respect to H3S10-phosphorylation, a mark normally associated with mitotic cells.

Taken together, we observed distinctive cell cycle changes and chromatin alterations in iALL cells exposed to the epigenetic modifier Vorinostat, compared to the micro-tubule inhibitor, Vincristine. Therefore, Vorinostat may act to induce global epigenomic reprogramming of iALL cells.

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

DRUG SENSITIVITY PROFILING, SYNERGY TESTING AND TRANSCRIPTOME ANALYSES IN INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA INDICATES PERSONALIZED RESPONSES TO THERAPEUTICS

Investigators: MN Cruickshank, J Ford, J Heng, RS Kotecha, and UR Kees, in collaboration with CH Cole, Haematology-Oncology, Princess Margaret Hospital.

Current multi-agent treatments have pushed the cure rate for some types of leukaemia to nearly 90%. For infants less than 18 months at the time of diagnosis, the survival rate is only 30%. Intensification of treatment protocols in infants has failed to improve survival but has resulted in large number of toxic deaths. We have generated a panel of eight cell lines derived from five patients with infant acute lymphoblastic leukaemia (iALL) and have subjected them to 101 approved cancer drugs at three doses, which is the first comprehensive assessment examining drug responses in iALL. Transcriptome analysis of these cell lines was examined by RNA-seq to identify gene expression and genetic variation.

Our primary drug screen clearly showed that most of the currently used drugs for iALL patients are not uniformly toxic to iALL cells, while other FDA-approved drugs were highly toxic at low doses, yet not used in contemporary protocols. Our data demonstrated heterogeneity in drug response among iALL cell lines. Despite this variability, we identified nine drugs that were commonly toxic to iALL cells. We next determined the 50% inhibitory concentration (IC50) of drugs of interest in 5 representative cell lines. Currently used drugs, effective drugs identified in the primary screen and several pre-clinical targeted compounds were examined. These results confirmed that currently used drugs (Dexamethasone, Prednisone, Hydrocortisone, Cytosine Arabinoside (ARA-C), Methotrexate, Thioguanine, 6-Mercaptopurine) generally showed high IC50 values and are thus unlikely to effectively treat iALL. In contrast, several effective drugs were identified that inhibit specific molecular processes such as histone deacetylases (HDACi) eg. Romidepsin and Panobinostat or proteasomes (PROTi) eg. Bortezomib and Carfilzomib. We further tested the hypothesis that HDACi or PROTi may sensitise iALL cells to currently used drugs. Our data revealed that PROTi and HDACi synergized with ARA-C or Dexamethasone, however these effects were patient-specific such that certain combinations were highly efficacious in only a sub-set of iALL cell lines. Further analysis of apoptosis and cell cycle perturbations after combinatorial drug treatments corroborated these findings and identified potential mechanisms of drug action.

Finally, transcriptome analysis of iALL cells at steady-state identified the expression level and functional genetic variation of genes involved in cell cycle/apoptotic pathways, DNA-repair and Notch and NF-kappa-B signaling.

Taken together, these results are consistent with clinical observations that a proportion of iALL patients are refractory to current drugs, including front-line steroid treatments. Moreover, we have identified classes of novel drugs (PROTi and HDACi) that are consistently effective against iALL. Importantly, synergy profiles of novel drugs with conventional iALL drugs revealed that combinatorial therapies improve cytotoxicity in a patient-specific manner. Thus, our data indicates that personalized therapies may be required for curative treatment for this aggressive cancer in infants.

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

TRANSCRIPTOME AND EXOME ANALYSES OF MLL-REARRANGED INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA IDENTIFIES, RECURRENT LOSS-OF-FUNCTION GENE VARIANTS INVOLVED IN DNA-REPAIR AND CELL CYCLE.

Investigators: AM Gout, RS Kotecha, J Ford, RW Francis, AH Beesley, MN Cruickshank and UR Kees.

Acute lymphoblastic leukaemia (ALL) occurring in the first year of life is rare, accounting for 2-5% of pediatric ALL cases. Infant ALL is distinguished by unique clinical and biological characteristics, with an aggressive course following a short latency period. The mixed lineage leukaemia (*MLL*) gene, located on chromosome 11q23, is involved in 80% of cases. Currently, 79 different *MLL*-fusion partner genes have been molecularly characterized with t(4;11), t(9;11) and t(11;19) the most frequent translocations in infant ALL. In this study we focused on *MLL*-rearranged infant ALL where diagnosis occurred at < 92 days. At present, the outcome for these infants remains poor with 26% five-year survival. Given the advent of next generation sequencing, further insight into the biology of the disease may identify potential targets for novel therapies and ultimately improve outcome.

We performed RNA-sequencing (Illumina, 100bp paired end) on 10 primary patient infant ALL samples including the common t(4;11) and t(9;11) rearrangements and a pair of monozygotic twins with a rare *MLL*-translocation partner gene, t(1;11). Matched DNA obtained from 7 patients during remission was subjected to exome-sequencing. RNA-seq and exome-seq reads were mapped to reference sequences (including genome, splice junction and transcriptome sequences for RNA-seq data) and variants were identified using a pipeline utilizing Genome Analysis ToolKit (GATK) functions. Variants were annotated using seven functional prediction algorithms (PolyPhen2, Sift, MutationTaster, likelihood ratio test, GERP, PhyloP and CADD), population allele frequencies (dpSNP, 1000 Genomes and HapMap) and presence in the Catalog of Somatic Mutations in Cancer (COSMIC variants).

We used a conservative "majority rule approach" described recently, whereby candidate non-synonymous variants are prioritized based on overlap of loss-of-function called by at least four of these computational methods. Ingenuity Pathway Analysis was performed on gene lists associated with predicted damaging SNVs. This revealed an over-representation of cell cycle and DNA-repair genes harboring damaging SNVs that were shared among three or more infant ALL patient samples. Furthermore, we examined the overlap of low minor allele-frequency (<1%) germ-line variants. Together, we found that these gene sets involved multiple genes previously reported to be involved with haematological neoplasia that may represent novel therapeutic targets for treatment. Finally, we sought to identify gene fusions in these datasets using FusionFinder that led to the identification of a number of novel putative gene fusions involving known oncogenes. Further studies are required to determine the role of these SNVs and gene fusions in infant leukaemogenesis.

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

Carcinomas

THE NUT MIDLINE CARCINOMA RESEARCH PROGRAM: UNDERSTANDING THE BIOLOGY OF A FATAL DISEASE

Investigators: A Stirnweiss, E Ferrari, AM Gout, RW Francis, UR Kees and AH Beesley, in collaboration with AK Charles, Princess Margaret Hospital, Perth.

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer that arises in various tissues along the midline of the body (e.g. thymus, thorax or abdomen) and can affect people of any age, including infants. Currently there is no effective therapy for NMC and median survival is less than seven months. The hallmark of the disease is a rearrangement of DNA that joins two genes (called BRD4 and NUT) to create a new hybrid gene that initiates and drives the cancer. Resolving how this *BRD4-NUT* fusion causes cells to grow out of control is a major aim of our research. Importantly, the *BRD4* gene is now implicated in a wide range of cancers and this work thus also contributes to our understanding of other diseases. To study this disease we have a rare panel of NMC cell lines grown from patients diagnosed at the Princess Margaret Hospital. To increase our understanding of the oncogenic mechanism in these NMC cells we undertook next-generation transcriptome sequencing (Illumina RNA-seq) of each line. To look for the expression of gene fusions, we developed an in-house program called *FusionFinder*, designed to detect transcripts containing sequences from two different genes. Analysis of the data from the NMC cell line PER-624 quickly identified a novel transcript in which Exon 15 of *BRD4* was fused to Exon 2 of *NUT*, therefore differing from all published NMC fusion transcripts. The three additional exons contained in the PER-624 fusion encode a series of polyproline repeats, with one predicted to form a helix. In the NMC cell line PER-403 we identified the 'standard' NMC fusion and two novel isoforms. Knockdown by siRNA in either cell line resulted in decreased proliferation, increased cell size and expression of cytokeratins consistent with epithelial differentiation. These data demonstrate that the novel *BRD4-NUT* fusion in PER-624 encodes a functional protein that is central to the oncogenic mechanism in these cells. Genomic PCR indicated that in both PER-624 and PER-403, the translocation fuses an intron of *BRD4* to a region upstream of the *NUT* coding sequence. Thus the generation of *BRD4-NUT* fusion transcripts through post-translocation RNA-splicing appears to be a common feature of these carcinomas that has not previously been appreciated, with the mechanism facilitating the expression of alternative isoforms of the fusion. Finally, ectopic expression of wildtype *NUT*, a protein normally restricted to the testis, could be demonstrated in PER-403, indicating additional pathways for aberrant cell signalling in NMC. These findings, published in the highly regarded journal Oncogene, increase our understanding of the diversity of NMC, and indicate that there are at least two molecular subtypes of the disease. Such knowledge is an important step towards finding therapeutic targets for a disease that is refractory to current treatments.

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

COMPARATIVE DRUG SCREENING IN NUT MIDLINE CARCINOMA: THE SEARCH FOR A CURE

Investigators: AH Beesley, A Stirnweiss, E Ferrari, UR Kees.

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer for which there is no effective therapy. Lack of progress in the development of treatment protocols for NMC is attributable both to the voracity of the disease and, until recently, difficulties in its diagnosis. Clinical protocols have essentially been adapted without systematic assessment, and so far with little success. The hallmark of the disease is a chromosomal translocation that disrupts a member of the bromodomain and extra-terminal (BET) protein family known as BRD4. Inhibitors that target BET proteins are currently in clinical trial for NMC but data from our laboratory indicate that these drugs are unlikely to be effective in all subtypes of the disease. To identify agents likely to be effective in NMC, we have performed a high-throughput drug screen against NMC cell lines in collaboration with the ACRF Drug Discovery Centre of Childhood Cancer (CCIA, Sydney). This involved comparative testing of the Prestwick Chemical Library of 1200 FDA-approved compounds in NMC vs. non-NMC cell lines. From this we have tested a shortlist of 15 compounds in a combinatorial fashion to identify those that may act synergistically in NMC cells. These represent a number of distinct drug classes including microtubule inhibitors, anthracyclines, topoisomerase inhibitors, antimetabolites, and anti-inflammatory agents, as well as BET inhibitors and the CDK9 inhibitor flavopiridol. In mice flank-engrafted with NMC cell lines, we have shown that flavopiridol treatment significantly decreases tumour growth and increases survival without toxicity, establishing the model with which to assess the in vivo efficacy of additional agents. The microtubule inhibitor vincristine also inhibited tumour growth and increased survival in these models, supporting the continued use of this class of agent to treat patients with NMC. These findings, recently published in the *British Journal of Cancer*, will now be extended in a larger panel of NMC cell lines that we have assembled from research groups and depositories around the globe. Such pre-clinical drug screening is an essential step towards finding effective treatment strategies for an orphaned disease that is refractory to current therapy approaches.

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

Brain Tumours

DEVELOPMENT OF A MOUSE EPENDYMOMA MODEL

Investigators: R Endersby, M Ancliffe, H Hii and NG Gottardo.

Ependymoma is the third most common brain tumour affecting children and remains incurable in 40% of patients. As is often the case with paediatric brain tumours, survivors are frequently left with devastating long-term neuro-cognitive sequelae. There is an urgent need for more effective and safer therapies. Transgenic mouse tumour models are important tools to facilitate the study of tumour initiation and progression and are invaluable for pre-clinical studies. A genome-wide analysis of human ependymoma specimens demonstrated that all cerebral ependymomas exhibited activated NOTCH signaling and *INK4A/ARF* deletion and that radial glia (RG) were the putative cell of origin of ependymoma. Based on these observations we generated the first mouse model of ependymoma, which phenocopies the human disease precisely by over-expressing *NOTCH1* in RG cells using the Blbp promoter and concurrent deletion of Ink4a/Arf. However, the penetrance of ependymoma formation was low (1 to 5%) with a long latency (6 to 18 months), suggesting that additional genetic mutations are required for ependymoma formation, making the current model unsuitable for pre-clinical testing. A more extensive genomic analysis using high resolution SNP genotyping of a larger cohort of human ependymoma specimens (n=230) revealed frequent focal deletions in the tumour suppressor gene *PTEN*. Array comparative genomic hybridisation analysis of mouse ependymomas demonstrated numerous large chromosomal copy number alterations (CAN) as well as focal CAN, common to all tumours, which included the *Pten* locus. Thus, to more faithfully recapitulate the human disease, we are modifying the existing ependymoma mouse model by additionally deleting *Pten*. The development of such a model will be an important tool to enhance our understanding of the biology of this disease and facilitate pre-clinical studies of novel targeted therapies.

This work is supported by the John Lillie Cancer Research Fellowship (RE and NGG).

MOLECULAR GENETICS OF NOVEL PAEDIATRIC BRAIN TUMOUR MODELS

Investigator: R Endersby

Brain tumours are the leading cause of death among paediatric neoplasms. The commonest malignant brain tumours of infancy and childhood are medulloblastoma (MB), pineoblastoma (PB) and ependymoma (ED). Despite recent therapeutic advances, the tumours in many patients relapse and are incurable. Moreover, survivors often have significant treatment-related sequelae. To develop more effective therapies, identifying and understanding the genetic events that drive these tumours is critical, as is deducing factors that contribute to therapeutic resistance.

MB, ED and possibly PB, are each comprised of multiple subgroups defined primarily by gene expression profiling. Additionally, a number of recent high-profile publications have further dissected the genetic complexity of MB using whole-genome (WGS) or whole-exome sequencing (WES). These data provide important new insights into the pathogenesis of MB and highlight targets for therapeutic development. However, whilst many targeted anti-cancer agents have recently been developed, evaluation of their efficacy is delayed due to a lack of model systems that accurately reflect the various subtypes of these diseases in children.

To address this, we have generated a panel of unique cell lines representative of various primary and relapsed paediatric brain tumours. Furthermore, to more closely resemble their natural microenvironment, we have established mouse models for these diseases by orthotopic transplant providing a unique resource in the

preclinical analysis of novel therapies. However, the preclinical utility of these new models requires full characterization of their underlying genetic alterations such that molecularly targeted therapies are assessed in the most appropriate systems.

Our study aim is to identify mutations across the coding regions of several new models of paediatric brain tumours using whole-exome capture and deep sequencing. With our models and the results of this study we will be poised to study critical questions about malignant brain tumour biology and be better able to test novel therapies in the most appropriate context.

This work is supported by the Telethon Kids institutional small grants scheme and The Telethon Adventures.

REPURPOSING APPROVED DRUGS TO TREAT CHILDHOOD BRAIN CANCER

Investigators: TD Schoep, R Endersby, JP McGlade, PB Dallas, NG Gottardo.

Brain tumours are the second most common cancer in children and are the major cause of childhood cancer related mortality. This highlights the fact that although survival for children with brain tumours has improved over the last 30 years, survival rates for the past decade have reached a plateau well below that of other childhood cancers, such as leukaemia. Moreover, children that do survive brain tumours suffer debilitating long-term side effects, which significantly impact on their quality of life. After surgery, residual tumour is treated with a combination of intensive chemotherapy and whole brain and spine radiation. However, this approach is devastating to children under three years of age as the radiation kills normal brain cells as well as tumour cells, which has a major impact on subsequent brain development. For this reason, children under three years old are not treated with radiotherapy. However, chemotherapy alone is rarely effective and the tumours in most of these patients grow back. There is therefore a clear need for novel therapies that increase survival rates. We are identifying drugs that when combined with conventional brain tumour therapies improve the outcomes for the most common childhood brain cancer, medulloblastoma (MB), and the rarer, but highly lethal brain cancer, pineoblastoma (PB). To achieve this, we are performing a high-throughput screen (HTS) using state of the art robotic technology, of thousands of compounds including existing FDA-approved drugs, other pharmaceuticals and known bioactive compounds with the aim of repurposing drugs for the treatment of these cancers. The advantage of repurposing existing drugs is that the pharmacokinetic profiles and toxicities have been extensively characterised, promoting rapid translation into the clinic. The efficacy of compounds will be evaluated alone and in combination with currently used conventional chemotherapeutics in vitro to identify optimal combinations. Their activity will then be validated in vivo using sophisticated animal models of MB and PB established in our laboratory to closely mimic the disease in children. As part of an international drug discovery network, in addition to our HTS approach for drug discovery we are also validating promising therapeutics identified at our drug discovery partner institution, St Jude Children's Research Hospital, in our unique animal models of MB and PB. Our dual approach of repurposing existing, FDA approved drugs for the treatment of childhood brain cancer, and validating new drugs discovered internationally ensures that the best molecules proceed to clinical trial in the shortest amount of time.

This work is in part supported by the NHMRC, John Lillie Fellowship (RE and NGG), Raine Clinician Research Fellowship (NGG), Elliot Parish Research Fellowship and Telethon Adventurers.

TESTING NOVEL CHEMOTHERAPEUTICS IN CHILDHOOD BRAIN TUMOUR MODELS

Investigators: R Endersby, JP McGlade, H Hii and NG Gottardo.

Whilst many novel targeted anti-cancer agents have been developed, there are few that are used clinically in paediatric brain cancer treatment. One reason is due to the lack of model systems that accurately reflect these diseases in which these novel drugs can be evaluated. Medulloblastoma (MB) and pineoblastoma (PB) are malignant embryonal brain tumors with a propensity to disseminate throughout the central nervous system. Despite significant improvements in therapy, many children remain incurable and survivors are often left with devastating late-effects, highlighting the need for innovative therapeutic strategies that target tumorigenic signaling pathways. To evaluate the efficacy of potential new therapies, as single agents and in combination with conventional chemotherapeutic drugs, we have developed *in vitro* models and orthotopic xenograft systems with a panel of cell lines derived from different MB subtypes and PB. In addition, this study utilises a transgenic spontaneous mouse model of MB, the *ND2-SmoA1* mouse, which represents the Sonic Hedgehog subgroup of human MBs. We hypothesise that the use of these models will accelerate the evaluation of novel treatment regimens that combine conventional chemotherapeutics with novel targeted agents.

Previous studies have revealed that over-expression of the transmembrane receptors *ErbB2* and *ErbB4* is associated with poor prognosis in children with MB, suggesting that inhibition of this pathway may be of therapeutic benefit.

Immunoblot and immunohistochemical analyses have determined that the ErbB pathway is deregulated in several of our *in vitro* and *in vivo* models as observed in children with MB, indicating that these are ideal systems to examine inhibitors of this pathway. We are therefore testing a novel irreversible pan-*ErbB* inhibitor, PF-00299804 (Pfizer Inc.), which has shown anti-tumor activity in lung cancers harboring deregulated ErbB family receptors.

Using our cell lines and standard cellular proliferation assays we have determined the sensitivity of brain tumour cells to conventional anti-cancer therapies currently used in the clinic for these tumours, including vincristine, cyclophosphamide, cisplatin and lomustine. We have subsequently investigated how PF-00299804 influences the anti-cancer activity of these drugs and identified synergism when this novel compound is combined with cyclophosphamide or cisplatin. This data has formed the basis for novel combinatorial

treatment regimens being tested in a pre-clinical trial using the orthotopic transplant models and the Smo MB model to determine if this is a potential candidate drug to propose for future clinical trials in a subset of patients with this disease.

This work is supported by the NHMRC, the John Lillie Cancer Research Fellowship (RE and NGG), Raine Clinician Research Fellowship (NGG), a grant from Pfizer Inc. and a Princess Margaret Hospital Foundation Translational Research Grant.

PRECLINCAL TESTING OF NOVEL TREATMENTS FOR PRIMITIVE NEUROECTODERMAL TUMOURS (PNETS)

Investigators: Arnaout A, McGlade JP, Hii H, Schoep TD, Gottardo NG and Endersby R.

One in five childhood cancers arise within the central nervous system. Primitive neuroectodermal tumours (PNETs) including medulloblastoma and pineoblastoma are the most common malignant brain tumours of childhood and survival rates are low compared to other paediatric cancers such as leukaemia. Current treatment protocols often fail and can leave children with devastating long term side effects, consequently there is a clear need for novel treatments for PNET.

Several high-throughput screens have been performed recently to identify new drugs that might be effective against PNET. One of these drugs was MK-2206 that targets the phosphatidylinositol-3-Kinase (PI3K) pathway downstream effector AKT, a ubiquitous and evolutionarily conserved signalling cascade influencing numerous cellular functions and frequently deregulated in human cancer. AKT isoform expression and the effects of MK-2206 on pathway activity in three pineoblastoma cell lines were evaluated using immunoblotting, which confirmed the drug inhibited the three AKT isoforms present in human cells. MK-2206 was also effective at inhibiting pineoblastoma cell proliferation as measured by alamar blue assay. Moreover, the ability of MK-2206 to modulate the anti-cancer activity of several conventional chemotherapeutics used in PNET treatment, such as cisplatin and vincristine, was assessed using drug interaction assays and biostatistical calculations. These studies revealed MK-2206 synergises with cisplatin to kill pineoblastoma cells *in vitro.*

In addition, the combination of pemetrexed (a folate antimetabolite) and gemcitabine (a DNA poison) has also recently been identified as a potential new treatment for PNET using *in vitro* high-throughput screening. This combination is a promising new treatment for non-small cell lung cancer. To evaluate the activity of this drug combination in PNET, immunodeficient mice were orthotopically implanted with human medulloblastoma cells. Despite having some impact on tumour cell proliferation and survival *in vivo*, no overall impact on animal survival was observed.

These studies reveal that high-throughput drug screening and *in vitro* assessment of novel drugs in paediatric brain tumour cells can identify potential new therapies for PNET and assessment of new drug combinations using preclinical models will inform which new treatments validate translation into novel clinical trials for childhood brain cancer.

This work is supported by the John Lillie Fellowship (RE and NGG), Raine Clinician Research Fellowship (NGG), Elliot Parish Research Fellowship and Telethon Adventurers.

ONCOGENIC TRANSFORMATION OF HUMAN NEURAL STEM CELLS.

Investigators: JP McGlade, R Endersby, PB Dallas and NG Gottardo.

Medulloblastoma is a malignant brain tumour that is the most common cause of cancer-related death in children.Recent studies have described at least four distinct subgroups of medulloblastoma based on their genetic characteristics. However, while specific genes have been associated with the development and progression of medulloblastoma, a direct causal relationship has yet to be established. Furthermore, the cell type(s) from which this cancer arises has yet to be identified. Evidence from animal models of medulloblastoma suggest that neural stem cells are a good candidate for investigating the cellular origin of this disease.

The aim of this pilot study is to transform normal human neural stem cells into cancer-causing cells by altering the expression of five specific genes implicated in medulloblastoma. These cancerous cells will then be implanted into the brains of mice and we will examine their potential to form medulloblastoma tumours.

This methodology has been successfully achieved in another brain tumour model (glioblastoma). This pilot grant will enable CI McGlade (Early Career Researcher) to extend this model to medulloblastoma.

This study will provide for the first time a direct test of whether previously identified candidate genes are involved in causing the development of medulloblastoma. In addition, this study will generate unique mouse models and identify potential new targets for therapy.

This work is supported by the Brain Foundation, the Telethon

THE CHARACTERISATION OF DEREGULATED MICRORNA EXPRESSION IN MEDULLOBLASTOMA

Investigators: LA Genovesi, JL Bearfoot, K Carter, NG Gottardo, and PB Dallas in collaboration with KM Giles of the Western Australian Institute for Medical Research, Perth.

MicroRNAs (miRNAs) are a large class of short non-coding RNAs that regulate growth and development in eukaryotic cells. It is now clear that deregulated miRNA expression plays an important role in the pathogenesis of many different types of cancer, including adult brain tumours. Recent data suggest that deregulated miRNA expression may also play a significant role in the pathogenesis of MB. To address this issue in more detail we analysed the expression levels of a panel of 754 miRNAs in MB specimens and neural stem cells (NSCs) using qRT-PCR in a low-density array format. We identified 33 differentially regulated miRNAs in primary specimens relative to CD133+ NSCs. Interestingly, several of the over-expressed miRNAs were predicted to target FOXO1A raising the possibility that down-regulation of FOXO1A expression in MB may be linked to deregulated miRNA expression. Several deregulated miRNAs

mapped to chromosome 14q32, and integrative analyses with inversely correlated predicted target genes revealed enrichment of pathways related to neuronal migration, nervous system development and cell proliferation. We also identified a link between deregulated expression of members of the mir-200 miRNA family, which are important regulators of epithelial-mesenchymal transition, in the more aggressive MB subtypes. We anticipate that ongoing research based on these data will rationalise our understanding of the fundamental molecular mechanisms that initiate and maintain the brain tumour phenotype.

This work was supported by the Raine Medical Research Foundation and Cancer Council of Western Australia.

NOVEL PEPTIDE BASED DRUGS FOR THE TREATMENT OF SONIC HEDGEHOG DEPENDENT MEDULLOBLASTOMA

Investigators: PB Dallas, TD Schoep, R Endersby, NG Gottardo, in collaboration with N Milech, B Longville, P Watt, R Hopkins, Drug Discovery Group, Telethon Kids Institute.

Medulloblastoma (MB) is the most common malignant brain tumour in children, and a leading cause of paediatric cancer related mortality and morbidity. Recently, drugs that target Smoothened (SMO), which is a component of the sonic hedgehog (SHH) pathway, have shown great promise for the treatment of MB. However, there are drawbacks with these new SMO targeting drugs, particularly associated with the development of resistance. Phylomers are a unique type of peptide-based drug developed by the drug discovery company Phylogica, which may be particularly suitable for avoiding the drug resistance problem, and may open new avenues for effective MB therapeutics that have yet to be exploited. In addition, Phylomers that are effective for the treatment of MB may also be effective for other types of cancer, including basal cell carcinomas, the majority of which are associated with altered SHH pathway activity. Preliminary data suggest that several Phylomers we have identified are capable of blocking SHH pathway activity *in vitro*. If the inhibitory activity of these Phylomers can be recapitulated *in vivo*, Phylomers may ultimately provide a new treatment option for MB patients.

This research is supported by the Telethon Adventurers.

Staff and Students

HEAD OF DIVISION

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Consultant, Department Haematology/Oncology, Princess Margaret Hospital for Children

RESEARCH STAFF

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Mani Kuchibhotla, MSc

POSTGRADUATE STUDENTS

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Julia Wells, BSc (Hons), PhD candidate

Mathew Ancliffe, BSc, Honours student

Laurence Cheung, BPharm (Hons), PhD

Other Students

Brooke Strowger, Murdoch University

Brett Patterson, UWA

Emma Downing, Perth Modern School

Jack Manera, Perth Modern School

THESES PASSED

Mathew Ancliffe (BSc), Honours thesis, Murdoch University, Generation of Novel Mouse Models for Paediatric Ependymoma

RESEARCH SUPPORT

Stewart Cattach

Awards

Nicholas Gottardo, Raine Clinician Research Fellowship (2013 – 2015).

Jacqueline McGlade, Telethon Institute for Child Health Research, Small Grant (2013, 1 year)

Jacqueline McGlade, Brain Foundation Research Gift (2013).

Brett Patterson, Cancer Council of Western Australia Summer Vacation Scholarship (2013-2014)

Alex Beesley, Children's Leukaemia and Cancer Research Foundation (CLCRF) Research Fellowship (2013): 'Targeting therapy and disease outcomes in NUT Midline Carcinoma' (3 years).

Alex Beesley, CLCRF Project Grant (2013): 'Morpholino therapy for childhood cancer' (1 year).

Alex Beesley, CLCRF Project Grant (2013): 'Finding the most effective therapies for midline carcinoma' (1 year).

Meegan Howlett, Children's Leukaemia and Cancer Research Foundation Travel Grant.

Mark Cruickshank, Children's Leukaemia and Cancer Research Foundation Travel Grant.

Nick Gottardo and Raelene Endersby, John Lillie Cancer Research Fellowship (2011-2014, 3 years)

Nick Gottardo, Raelene Endersby and Ursula Kees, NHMRC Project Grant APP1033720 (2012-2014, 3 years) Testing novel therapies using paediatric brain tumour models.

Ursula Kees, Alex Beesley, Adrian Charles, NHMRC Project Grant ID1007586 (2011-2014): Role of connective tissue growth factor in the pathobiology of lymphoid tumours and response to therapy.

Ursula Kees, Richard Lock, Alex Beesley, NHMRC Project Grant ID1011499 (2011-2014): Targeting drug-resistance in paediatric acute lymphoblastic leukaemia.

External Committees

INTERNATIONAL

Ursula Kees, Chair COG-B969 Study Committee (Children's Oncology Group), Arcadia, CA USA.

Nicholas Gottardo, Children's Oncology Group (COG). Central Nervous System Tumour Committee

Nicholas Gottardo, international conference convenor, Global Symposium on Childhood Brain Tumours. February 11-14, 2013. Bunker Bay, Australia.

Nicholas Gottardo. Study Chair for the upcoming COG Average Risk Medulloblastoma front-line clinical trial.

Nicholas Gottardo. Medical Advisory Committee. The Cure Starts Now Foundation.

Raelene Endersby, international conference organising committee, Global Symposium on Childhood Brain Tumours. February 11-14, 2013. Bunker Bay, Australia.

Nicholas Gottardo, international conference organising committee for the premier paediatric Neuro-Oncology conference: International Symposium on Paediatric Neuro-Oncology, Singapore, 2014.

NATIONAL

Nicholas Gottardo. Co-chair on currently open paediatric phase I/II clinical trial conducted through the ACCT entitled: A Phase I/II Study of Valproate in Combination with Interferon alpha in Relapsed, Recurrent or Progressive Neuroblastoma.

Nicholas Gottardo. Executive Councillor on the Australian and New Zealand Children's Haematology/Oncology Group Executive (2012-present)

Raelene Endersby, national conference organising committee, Science Pathways: Linking Academia with Industry. October 2013. Melbourne, Australia.

LOCAL

Ursula Kees, The Cancer Council of Western Australia, Research and Scientific Advisory Committee.

Nicholas Gottardo, Member of WA Health Department Rare Diseases Strategy Advisory Group

Raelene Endersby, Australian Cancer Research Foundation Cancer Imaging Facility, Management Committee.

Invited Presentations

Alex Beesley (February 2013). Interrogating NUT midline carcinoma – an aggressive and fatal cancer. Lorne Cancer Conference, Victoria, Australia.

Mark Cruickshank (July 2013). Targeting the epigenetic machinery in infant acute lymphoblastic leukaemia therapy. Perth Cancer Club, Perth, WA.

Ursula Kees (October 2013). Pathophysiology of CTGF/CCN2 expression in acute lymphoblastic leukaemia. Seventh International Workshop on the CCN Family of Genes, Nice, France

Meegan Howlett (October 2013). High levels of connective tissue growth factor/CCN2 can accelerate disease in a model of acute lymphoblastic leukaemia. Seventh International Workshop on the CCN Family of Genes, Nice, France.

Alex Beesley (October 2013). Researching childhood cancer. Rotary-Lions Club South West Bike Trek Fundraiser, Pinjarra, WA.

Alex Beesley (October 2013). When the drugs don't work - High-throughput screening of therapy options for a fatal carcinoma. Cancer Council WA Symposium, Perth, Western Australia.

Laurence Cheung (October 2013). Expression of CTGF in acute lymphoblastic leukaemia disturbs the bone marrow microenvironment. Eighth State Cancer Conference, Cancer Council Western Australia, Perth, WA.

Julia Wells (October 2013). Connective tissue growth factor is increased in acute lymphoblastic leukaemia and confers a growth advantage within the bone marrow niche. Eighth State Cancer Conference, Cancer Council Western Australia, Perth, WA.

Mark Cruickshank (November 2012). Troubleshooting & tools for HM450 methylation array analysis using twins and longitudinally

sampled Guthrie card blood spots. WA Genomics & Epigenomics interest group. Perth, Australia.

Nicholas Gottardo, invited speaker, Children's Oncology Group meeting, USA, 2013

Nicholas Gottardo, The Children's Oncology Group's (COG) frontline average risk medulloblastoma clinical trial. Medulloblastoma Down Under, Bunker Bay, Australia, Feb 2013

Raelene Endersby, Model systems for studying paediatric brain tumours: How to maximise outcomes in translational research. Preclinical Imaging Workshop: Radiopharmaceutical, MRI & Optical Imaging in Experimental Oncology & Neurology. Perth, Australia, Nov 2013.

Raelene Endersby, Deciphering the genetics of adult and paediatric brain tumours. Brain Tumour Expo. Perth, Australia, Nov 2013.

Raelene Endersby, There & Back Again: Experiences of Doing a Postdoc Abroad. 23rd Annual Combined Biological Sciences Meeting. Perth, Australia, Aug 2013.

Raelene Endersby, Childhood brain tumours: from bedside to bench and back. Western Australian Institute for Medical Research, Perth, Australia, June 2013.

Raelene Endersby, Childhood brain tumours: from bedside to bench and back. University of WA, Department of Pathology and Laboratory Medicine. Perth, Australia, June 2013.

Raelene Endersby, The search for the Holy Grail in childhood brain tumour therapy. Australian & New Zealand Children's Haematology/Oncology Group Annual Scientific Meeting. Melbourne, Australia, May 2013.

Peter Dallas. The development of novel peptide based drugs for the treatment of sonic hedgehog dependent medulloblastoma and other cancers. Eighth State Cancer Conference. Perth WA, Oct 2013.

ACTIVE collaborations

Prof M Norris & Prof M Haber. Experimental Therapeutics Program, Children's Cancer Institute Australia for Medical Research

Prof R Lock, Leukaemia Biology Program, Children's Cancer Institute Australia for Medical Research

Dr Richard Lipscombe, Proteomics International, Perth, Australia.

Metabolomics Australia, University of Western Australia, Perth, Australia

Prof C Mullighan St Jude Children's Research Hospital, Memphis TN, USA

Prof W Alexander and Dr R Dickins, Walter and Eliza Hall Institute of Medical Research, Melbourne

Prof D Brigstock, Children's Research Institute, Columbus OH, USA

Dr M Garnett, Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, UK

Dr G. Arndt, ACRF Drug Discovery Centre for Childhood Cancer, Children's Cancer Institute Australia for Medical Research, Sydney

Prof C. Cole, Dr M Phillips, Dr T Carter and Dr A Charles, Department of Paediatric and Adolescent Haematology and Oncology, Princess Margaret Hospital for Children

Novartis Pharma AG, Basel, Switzerland, NMC Carcinoma Project

GlaxoSmithKline R&D, Brentford, UK, NMC Carcinoma Project

Dr Christopher French, Women and Brigham's Hospital, Boston

Dr A Murch, Cytogenetics Department, King Edwards Memorial Hospital, Perth

Dr Bernard Callus, School of Chemistry and Biochemistry, University of Western Australia, Perth

Prof Peter Leedman and Dr Keith Giles, Western Australian Institute of Medical Research, Perth

Prof Terry Johns, Monash Institute for Medical Research, Melbourne.

Pfizer Inc, New York, USA

Professor Steve Wilton, Foundation Chair in Molecular Therapies, Centre for Comparative Genomics, Murdoch University.

Dr James Bradner, Dana-Farber Cancer Institute, Harvard Medical School, Boston USA.

Dr Ester Falconer, Terry Fox Laboratory, BC Cancer Research Centre, Vancouver BC, Canada.

Prof Ryan Lister, University of Western Australia, Perth, WA.

Dr Alistair Forrest, Ricken, Facility Director / Unit Leader - LSA Bioinformatics Core Facility, Yokohama Institute, Japan.

Brain Cancer Discovery Collaborative, members: Prof Terrance Johns (MIMR-PHI Institute of Medical Research, VIC), Prof Andrew Boyd (QIMR Berghofer Medical Research Institute, QLD), Dr Kerrie McDonald (Lowy Cancer Research Centre, NSW), Dr Nicholas Gottardo (Telethon Kids Institute, WA), Assoc Prof Stephen Rose (CSIRO, QLD), Assoc Prof Geraldine O'Neill (Children's Hospital at Westmead, NSW).

International Medulloblastoma Working Group (50 members)

Prof Amar Gajjar, St Jude Children's Research Hospital, USA

Dr Suzanne Baker, St Jude Children's Research Hospital, USA

Dr Charles Eberhart, Johns Hopkins Medicine, USA

DIABETES AND OBESITY RESEARCH

Overview

The team conducts research in collaboration with the Department of Endocrinology and Diabetes in Princess Margaret Hospital for Children Perth, the School of Sports Science and Exercise Health, Psychology, University of Western Australia; the Western Australian Institute for Medical Research, the Juvenile Diabetes Research Foundation and collaborators from diabetes research centres interstate and overseas Our primary research is in the field of Type 1 diabetes. We are also increasingly involved in research into childhood onset Type 2 diabetes and obesity with the aim of improving the lives of children and adolescents affected by these conditions. Our research addresses relevant clinical questions and encompasses epidemiology, clinical investigations, clinical trials, new technology in disease management and prevention studies.

In the year 2013, type 1 diabetes research has seen the advancement in a series of clinical trials with the ultimate aim of implementing the closed-loop system to improve glycaemic management in Type 1 diabetes using pump therapy.

The Group has published papers in the areas of exercise and type 1 diabetes, psychological impact of hypoglycaemia in type 1 diabetes, pump therapy in type 1 diabetes, sensor augmented pump therapy in type 1 diabetes, mortality risk in type 1 diabetes, environmental determinants of type 1 diabetes (methods paper), microvascular function in type 1 diabetes and the management of obesity.

TYPE 1 DIABETES

Clinical Prof TW Jones, Associate Clinical Prof EA Davis

Epidemiology

EPIDEMIOLOGY OF CHILDHOOD-ONSET TYPE 1 DIABETES IN WESTERN AUSTRALIA

Liz Davis, Aveni Haynes, Matt Cooper, Carol Bower

The objectives of this study are:

- To study the epidemiology of childhood onset diabetes in children aged 0-16 years in Western Australia from 1985 onwards.
- To test for differences in incidence rates by year of diagnosis, age of diagnosis, sex, month of diagnosis, birth month and place of residence at diagnosis.
- To identify potential antenatal and perinatal antecedents to childhood-onset diabetes e.g. birth weight, gestational age, birth order and maternal age.

These aims will be achieved by means of data linkage using the Western Australian Children's Diabetes Database, and Western Australian Midwives' Notification System . The study population will be all children diagnosed with childhood-onset diabetes before the age of 15 years, who were resident in Western Australia at the time of diagnosis. The study period will be from January 1985 to December 2010. There are over 1500 cases in the diabetes register at Princess Margaret Hospital that meet these inclusion criteria. Cases in the Western Australian Children's Diabetes Database at Princess Margaret Hospital will be linked to records in the Western Australian Midwives' Notification System using the unique personal identification number assigned to individuals in the Western Australian Health Department databases.

Funding Source: Department of Endocrinology & Diabetes, PMH

EPIDEMIOLOGY OF HYPOGLYCAEMIA IN CHILDHOOD-ONSET DIABETES IN WESTERN AUSTRALIA

Tim Jones, Liz Davis, Matt Cooper

Hypoglycemia and the subsequent effects of hypoglycemia remain the primary fear for children and their parents in adequately managing the treatment of Type 1 Diabetes (T1D). It is reported that over the past decade the overall incidence of severe hypoglycemic events has declined relative to the previous decade. In this study we investigate the demographic, lifestyle and diabetes management factors associated with the incidence of severe hypoglycemia to provide clinicians and diabetes educators with knowledge our which patients may be at higher risk of severe hypoglycemia.

The aims of this study are:

- Report the incidence of severe hypoglycemia over the past decade in the WA childhood T1D onset cohort
- Calculate the relative risk for the association of demographic, lifestyle and management factors (including but not limited to age, length of diagnosis, BMI, insulin regime) with the incidence of severe hypoglycemia.

Funding Source: Internal Funds

INVESTIGATING MORTALITY RATES AND THE INCIDENCE AND RISK FACTORS OF DIABETES COMPLICATIONS AND CO-MORBIDITIES DURING EARLY ADULT LIFE IN A POPULATION BASED CHILDHOOD ONSET DIABETES COHORT

Investigators: Liz Davis, Matt Cooper, Aveni Haynes, Tim Jones

The education and treatment regimes for children with Type 1 Diabetes (T1D) are constantly evolving, and the introduction of and improvements to new technologies adds to the complexity of the management of T1D. Studies have been done in the past to provide insight into the complications and co-morbidities in adulthood for this with childhood onset type 1 diabetes, but little is known about how the changes to diabetes management affect the incidence of these complications and co-morbidities, as this is something that can only be revealed with time. This project will use the Western Australian Data Linkage System (WADLS) to provide novel information of the incidence and relative risk of T1D co-morbidities and mortality during early adulthood in a modern clinical setting. The primary source of the study population is the Western Australian Children's Diabetes Database. The WADLS contains data uploaded from the Hospital Morbidity Data Collection; the Emergency

Department Data Collection; the Mental Health Information System; the Birth, Death and Marriages Registry and the Western Australia Electoral Commission records. The WADLS will enable the selection of matched controls from the birth registry. All subjects in WA diagnosed with T1D prior to age 16 who were 18 years or older at 30th June 2010 (n=1,376) are considered eligible for entry into this analysis.

The aims of this study are:

- To identify the incidence of diabetes complications and co-morbidities seen in early adulthood (<40 years) in a childhood onset T1D population-based cohort.
- To calculate the risk (relative to age and sex matched controls) for incidence of diabetes complications and co-morbidities in early adulthood (<40 years) associated with childhood onset T1D in a population-based cohort.
- To compare the all-cause mortality rate, and cause of death in early adulthood (<40 years) in a childhood onset T1D population-based cohort to general population age and sex matched controls.
- To examine the impact of risk factors observed during childhood on the incidence of diabetes complications, co-morbidities and cause of death in early adulthood (<40 years) in a childhood onset T1D population-based cohort.

Funding Source: Diabetes Research Fund

TRIALNET: PATHWAY TO PREVENTION

Local Investigators: Tim Jones, Liz Davis

Study Staff: Julie Dart, Heather Roby; Adam Retterath;

The overall objective of this multi-centre international study is to perform baseline and repeat assessments over time of the metabolic and immunologic status of individuals at risk for type 1 diabetes (T1D). This is in order to:(a) characterize their risk for developing T1D and identify subjects eligible for prevention trials, (b) describe the pathogenic evolution of T1D, and (c) increase the understanding of the pathogenic factors involved in the development of T1D.

The specific objectives of this study are:

To determine the risk for the occurrence of T1D according to glucose tolerance tests, C-peptide levels, islet autoantibodies, HbA1c levels, markers of cell-mediated immunity, and genetic markers associated with T1D.

To examine the accuracy of TrialNet measures in predicting future T1D.

To characterize the progression of immunologic abnormalities in the development of T1D by serially studying islet autoantibodies and immune mechanistic studies.

To characterize the progression of metabolic decompensation in the development of T1D by serially studying insulin, C-peptide, other islet hormones, HbA1c and glucose levels, and to identify immunologic and other factors associated with this decompensation.

5. To determine the incidence of severe acute metabolic decompensation as the initial clinical presentation in individuals who have been identified as being at increased risk for T1D.

6. To identify individuals who qualify for TrialNet T1D prevention trials.

7. To accrue additional information about immunologic and metabolic factors related to the pathogenesis of T1D and validate new methods or tests that mark disease progression or response to therapy.

8. To accrue additional information about genomic markers associated with risk for the development of T1D.

9. For those participants who participated in the DPT-1 study, to examine associations of characteristics (e.g. demographics, immunologic, metabolic, etc.) assessed during the DPT-1 study with characteristics and outcomes assessed in TrialNet.

The primary outcome of this prospective cohort study is the development of diabetes as defined by the American Diabetes Association (ADA) based on glucose testing, or the presence of symptoms and unequivocal hyperglycaemia.

Participant eligibility: (1) Having a first degree relative (parent, sibling, child) with T1D, and aged 1 – 45 years; (2) having a second and third degree relative (nieces, nephews, aunts, uncles, grandparent, cousins, half-siblings) with T1D and aged 1 – 20 years.

Funding Source: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation International (JDRF), and the American Diabetes Association (ADA)

EARLY ENVIRONMENTAL DETERMINANTS OF PANCREATIC ISLET AUTOIMMUNITY: A PREGNANCY TO EARLY LIFE COHORT STUDY IN CHILDREN AT RISK OF TYPE 1 DIABETES (T1D)

Local Investigators: Tim Jones, Liz Davis

Study Staff: Wayne Soon

This is a multi-centre study involving researchers in South Australia, Victoria, New South Wales, Western Australia and Queensland. The study is coordinated by Prof Jenny Couper in South Australia.

This prospective cohort follows children who are at risk of developing T1D from the gestational period into the first 3 years of life. Pregnant women who have type 1 diabetes or where their unborn child has a first degree relative with T1D are recruited to the study. The infants are monitored for genotype, weight gain, insulin sensitivity, changes in the metabolome and microbiome, vitamin D and omega 3 fatty acid status, and the timing and frequency of viral infections. This is in order to determine the relationship between weight gain, insulin sensitivity, nutritional status and viral infection, and the development of persistent islet autoimmunity in these children.

The primary outcome measure is islet autoimmunity defined as persistent elevation of > 1 islet autoantibodies on consecutive 6

monthly tests, including the most recent. This will exclude transient, low titre autoantibodies.

Funding Source: NHMRC 1025082

Management

HOW DO HIGH PROTEIN AND/OR HIGH FAT MEALS AFFECT POSTPRANDIAL GLYCAEMIC CONTROL IN CHILDREN USING INTENSIVE INSULIN THERAPY?

Local Investigators: Liz Davis;

Study Staff: Megan Evans

This dual-site study is investigating the effect of fat and protein content of a standardized carbohydrate meal, on the post-prandial glycaemic response in children with type 1 diabetes who are on multiple daily injections or insulin pump therapy. The study design is a randomised 4 armed cross-over trial, where the glycaemic fluctuations in the 180min following the meal is traced using a continuous sub-cutaneous glucose monitoring system. investigating the

58 children between the two participating sites having the following inclusion criteria, will be recruited: aged- 7-18 years inclusive; on 4 or more insulin injections per day, or on insulin pump therapy; diagnosed with type 1 diabetes, at least over 6 months ago; with HbA1c ≤ 8.0% at last clinic visit. Exclusion criteria are: Coeliac disease; Hyperlipidaemia; history of poor compliance or attendance; Unable to commit to full study protocol.

Funding Source: Pfizer APEC Research Grant

LOW GLUCOSE SUSPEND STUDY

Investigators: Tim Jones

Study Staff: Jennifer Nicholas, Adam Retterath

A new pump has just been released, the Paradigm Veo pump. This pump has the new feature of detecting low glucose levels (hypoglycaemia) and automatically switching off insulin infusion for 2 hours if the blood glucose level is low. This will be helpful in reducing the severity of an episode of hypoglycaemia.

The aim of this study is to see if using the Paradigm Veo pump for a period of 6months can reduce the rate of severe hypoglycaemia, particularly for patients who have lost some of the symptoms that would normally alert them to a low blood glucose level. In a subgroup of 16 adolescents, we will also look at their hormone and symptom responses during hypoglycaemia.

Patients aged between 4 years and 50 years with T1D on insulin pump therapy with impaired awareness of hypoglycaemia will be eligible to participate.

Patients will be randomised to either the Paradigm Veo (low glucose suspend feature and continuous glucose monitoring) or continue on their standard pump (no low glucose suspend capability and no continuous glucose monitoring).

Funding Source: Juvenile Diabetes Research Foundation

EFFECT OF EXERCISE INTENSITY ON THE RATE OF GLUCOSE ADMINISTRATION REQUIRED TO MAINTAIN STABLE GLYCAEMIA WHEN PLASMA INSULIN IS AT BASAL LEVELS IN INDIVIDUALS WITH TYPE 1 DIABETES MELLITUS

Investigators: Vinutha Shetty, Paul Fournier, Tim Jones, Liz Davis

Study Staff: Nirubasini Paramalingam, Adam Retterath, Heather Roby; Ray Davey; Kaitie McNamara

Regular exercise provides a number of well documented health benefits for individuals with type 1 diabetes. Unfortunately for individuals with type 1 diabetes, particularly those in good glycaemic control, exercise increases the risk of severe hypoglycaemia. This increased risk of hypoglycaemia occurs not only while exercising, but also for several hours during recovery. One approach to reduce the risk of hypoglycaemia associated with exercise is to reduce insulin dose before exercise. Another is to consume extra carbohydrates during and/after exercise, but the current guidelines for treatment of hypoglycaemia do not provide practical information about the amount of CHO necessary to prevent hypoglycaemia during exercise.

This proposed study aims to determine more precisely the amount of glucose intake that is required to prevent hypoglycaemia during exercise; under basal insulin conditions. In addition, we will investigate how glucose requirements are affected by exercise intensity and how this relationship responds to confounding factors such as prevailing insulin and glucose levels. This study will involve ten healthy, active type 1 diabetic individuals (male and female) aged between 13 and 25 years old. All participants will undergo four testing sessions involving cycling on a stationary bike at four different workloads – 35%, 50%, 65% and 80% VO2 peak.

Primary outcome: Calculation of the glucose requirements to maintain stable glucose levels during and after exercise over a range of exercise intensities under basal insulin conditions.

Secondary outcome: Determining the extent to which changes in glucose requirements result from changes in glucose production and utilisation rates.

Funding Source: Pfizer APEC Research Grant; PMH Foundation Grant

EFFECT OF ANTECEDENT HYPOGLYCAEMIA ON THE HYPERGLYCAEMIC EFFECT OF A SHORT 10-SECOND SPRINT IN TYPE 1 DIABETES

Investigators: Paul Fournier, Ray Davey; Tim Jones, Liz Davis

Study Staff: Nirubasini Paramalingam, Heather Roby

To investigate whether experiencing a low blood glucose event prior to a 10-second sprint reduces the capacity of the sprint to increase blood glucose levels in people with type 1 diabetes. Individuals with type 1 diabetes aged between 15 and 25 years will be recruited from the general population and from the population of individuals regularly attending diabetes clinics at Princess Margaret Hospital. All participants

must be free of any complications associated with type 1 diabetes.

All participants will be asked to visit our laboratory on four separate occasions. On two of these visits, the participants will be fitted with glucose and activity monitors to record data in the lead up to the study days. Each of the two study days will follow these preliminary data collection periods. On these visits, glucose and insulin will be infused to control the participants' blood glucose levels. On one occasion, their blood glucose will be lowered and kept at a low level for 90 minutes before it is returned to normal levels. On the other occasion, their blood glucose will be kept at normal levels during this 90-minute period and afterwards. Following each treatment, the participants will perform a 10-second sprint on an exercise bike. The participants will then rest for 2 hours and their blood will be taken at regular intervals to monitor their blood glucose levels and to measure hormone levels.

Funding Source: NHMRC

THE EFFECT OF HYPERGLYCAEMIA ON THE RATE OF GLUCOSE ADMINISTRATION REQUIRED TO MAINTAIN STABLE GLYCAEMIA DURING MODERATE INTENSITY EXERCISE IN INDIVIDUALS WITH TYPE 1 DIABETES MELLITUS

Investigators: Vinutha Shetty; Paul Fournier, Tim Jones, Liz Davis

Study Staff: Adam Retterath; Nirubasini Paramalingam, Heather Roby; Ray Davey

The aims of this are (1) To determine if hyperglycaemia prior to and during exercise, affects the amount of glucose necessary to maintain stable blood glucose levels (BGL) during moderate intensity exercise,

(2) To determine if hyperglycaemia prior to and during exercise, affects specific hormonal responses during and after moderate intensity exercise.

The hypothesis is that under basal insulin conditions, the amount of intravenous glucose required to maintain stable BGL during moderate-intensity exercise is increased during hyperglycaemia compared with euglycaemia.

All participants, with T1DM, aged between 13 and 25 years old (n=10), HbA1c < 9.5% and diagnosis of diabetes >1yr, will have two testing sessions and an initial session to determine their maximum exercise capacity. Testing sessions begin at 8am, and participants arrive having fasted overnight. A cannula is inserted in the back of one hand for blood sampling, and the elbow for infusion of insulin and glucose. In one session participants are asked to exercise at 50% of their VO2peak (moderate intensity exercise) after a stabilisation period during which their BGL is maintained between 4.5 to 5.5mmol/L (euglycaemia). In the alternate condition participants are asked to exercise at 50% of their VO2peak (moderate intensity exercise) after a stabilisation period which includes a period where their BGL is maintained between 8.5 - 9.5mmol/L (hyperglycaemia).

Their BGLs are maintained at these specified levels during exercise (euglycaemia or hyperglycaemia) by infusing 20%(w/v) dextrose solution. Urine will also be collected throughout these testing session in order to measure any glucose spill over, and this result will be used to track how the body uses the glucose infused. The amount of glucose oxidised during exercise is determined by the rate of oxygen consumption and CO2 production obtained by analysing samples of expired air collected from the subjects before, during and after exercise, at regular intervals using indirect calorimetry. Finally, since all these processes are under tight hormonal regulation, blood will be sampled at timed intervals for hormone assay. Participants will be provided a late lunch before leaving the laboratory, and will carry carbohydrates for hypoglycaemia treatment on the way home. They will also be asked to closely monitor their blood glucose levels for a day following the testing session.

Funding Source: NHMRC

THE EFFECT OF A 10-SECOND SPRINT ON THE COUNTERREGULATORY RESPONSES TO A SUBSEQUENT EPISODE OF HYPOGLYCAEMIA IN MALES AND FEMALES WITH TYPE 1 DIABETES MELLITUS.

Investigators: Ray Davey; Paul Fournier, Tim Jones, Liz Davis

Study Staff: Nirubasini Paramalingam, Heather Robyn

To determine if performing a 10-second sprint in the morning lessens the release of hormones to afternoon hypoglycaemia.

Both male and female participants with type 1 diabetes, aged between 13 and 30 years old will be recruited to this study. They will be in reasonable to good control of their diabetes and they will be aware of the symptoms of hypoglycaemia.

All participants will have two testing sessions and two pre-testing visits. Three days prior to each testing session, the participants will briefly visit the laboratory to have a glucose sensor and accelerometer fitted. These devices will measure their glucose levels and activity levels for 3 days before each study. Testing sessions will begin at 8am and the participants will arrive having fasted overnight. Two drips will be inserted; one to sample blood and the other to infuse glucose and insulin. Blood glucose levels will be kept at 5.5 mmol/L by varying the infusion rates of insulin. When blood glucose levels are stable, the participants will perform either a 10-second sprint or rest. Then, approximately 4 hours later, the participants will have their blood glucose level lowered over 30 minutes to 2.8 mmol/L by adjusting the infusion rate of glucose; at a higher rate of insulin. This blood glucose level will be maintained for a further 40 minutes before it will be increased to 5.5 mmol/L once more. At certain times before and after the sprint (or rest) and before and during the lowering of blood glucose levels, blood samples will be collected to measure blood glucose, insulin and key hormones that are released in response to hypoglycaemia. After this, the participants will have the drips removed and will be provided with lunch before they leave the laboratory. At least 2 weeks later, the participants will return to the laboratory to perform the alternate condition such that all participants perform both the morning sprint and the morning rest before they undergo afternoon hypoglycaemia on both

occasions.

Funding Source: NHMRC

Technological Advances

PREDICTIVE LOW GLUCOSE SUSPEND STUDY – STAGE 1

Local Investigators: Liz Davis; Tim Jones; Mary Abraham

Study Staff: Ray Davey; Jennifer Nicholas; Nirubasini Paramalingam; Adam Retterath; Julie Dart;

The availability of continuous glucose monitoring systems is an important advancement in the pursuit of a fully automated closed-loop system. An initial stage in the development of such a system has been the availability of a system that automatically suspends basal insulin delivery for a pre-determined period if patients do not respond to alarms. Whilst this is a major step forward, the capacity to suspend insulin delivery when impending hypoglycaemia is predicted offers the additional advantage of reducing the actual time spent hypoglycaemic. If effective and safe this system is likely to reduce the burden of diabetes care as well as allow more intensive attempts to improve glycaemic control.

This study will aim to test a novel algorithm for hypoglycemia prediction, under conditions of excess insulin and moderate intensity exercise, to determine if the response of insulin suspension to these different conditions which predispose hypoglycaemia differs. Crucial to the effectiveness of a preventive system and the prevention of post suspend hyperglycemia will be a complimentary algorithm that activates the resumption of insulin delivery. By studying post suspend glucose values under controlled conditions we will generate such data. In addition, although previous studies have utilized increased basal insulin delivery as a method of inducing hypoglycaemia, in our study we will utilize increased bolus insulin delivery-the scenario more likely to be encountered in a real-life setting.

Study participants will be: adolescents and young adults age from 12 to 26 years with type 1 diabetes; duration of diabetes > 1 year and on treatment with an insulin pump; HbA1c < 8.5%

The aims of this study are:

1. To determine the blood glucose profile with a predictive low glucose suspend (PLGS) algorithm versus no insulin suspension (control) following hypoglycemia induced by a bolus of subcutaneous insulin;
2. To determine the blood glucose profile with a PLGS algorithm versus no insulin suspension (control) following hypoglycemia induced by moderate intensity exercise;
3. To determine the blood glucose profile with a predictive low glucose management (PLGM) algorithm versus no insulin suspension (control) following hypoglycaemia induced by an increased basal insulin infusion overnight;
4. To analyse the pattern of blood glucose and ketone levels following pump suspension in these scenarios, and use these to assist with determination of parameters for insulin pump resumption.

Funding Source: JDRF

CLOSED LOOP STUDY – TREAT TO RANGE

Local Investigators: Martin de Bock; Tim Jones; Liz Davis;

Study Staff: Julie Dart; Adam Retterath; Jennifer Nicholas

The aim of this study is to see if the Portable Glucose Control System (PGCS), a portable artificial pancreas, is safe and accurate in managing blood glucose levels for a patient with type 1 diabetes during the day and night. The PGCS consists of 2 glucose sensors that sit under the skin, an insulin pump that delivers insulin and a BlackBerry phone. The Blackberry works out how much insulin to give by a special mathematical formula. The Blackberry receives a signal from the sensors and then tells the pump how much insulin to give.

At night, the PCGS will do everything for the patient. During the day, it will only work if the blood glucoses are very high or very low. The patient still continues to operate the pump as they normally would. We will also compare how well the system works with a night in hospital when the patient would manage their diabetes as they do at home.

There are 3 parts to this study and there will be 8 patients recruited to each part. Patients may take part if they have type 1 diabetes, be aged between 12-50 years and be on insulin pump therapy.

For the first part, we want to see how well the system manages patients going about their normal routine (Part 1). We will then go on to test how well the system manages high blood glucose levels when a dose of insulin is missed (Part 2) and how well it manages low blood glucose levels when they exercise (Part 3).

Funding Source: NHMRC

OVERNIGHT GLUCOSE CONTROL WITH AN ANDROID-BASED AUTOMATED AMBULATORY GLYCEMIC CONTROLLER (AAGC) IN PATIENTS WITH TYPE 1 DIABETES

Local Investigators: Martin de Bock; Tim Jones; Liz Davis;

Study Staff: Julie Dart; Adam Retterath;

The aim of this study is to see if the Automated Ambulatory Glucose Controller (AAGC), a portable artificial pancreas, is safe and reduces the time spent with low blood glucose levels in patients with type 1 diabetes at night in the patient's home environment. The AAGC consists of a glucose sensor that sits under the skin, an insulin pump that delivers insulin and an Android-based smartphone that contains the AAGC controller software. The AAGC works out how much insulin to give by a special formula. The AAGC receives a signal from the sensors and then tells the pump how much insulin to give. The maximum amount of insulin that would be given per hour would not be any greater than the pre-programmed rates that patients are already giving themselves.

Patients will firstly wear a glucose sensor for one week whilst they continue their standard diabetes care. This records their blood glucose values continuously and will give us a time to compare how well the AAGC works in reducing

hypoglycaemia.

Patients will then be admitted for one night in hospital. They will have the AAGC system fitted and the system will manage their blood glucose levels overnight. This will allow them to check to see if the glucose sensor is reading accurately. If it is, the system will continue to manage glucose levels till the morning.

Patients will be discharged home the following morning.

Funding Source: NHMRC

Complications

ADOLESCENT TYPE 1 DIABETES CARDIO-RENAL INTERVENTION TRIAL

Local Investigators: Tim Jones; Liz Davis

Study Staff: Alison Roberts; Vinutha Shetty; Mary Abraham; Martin de Bock; Adam Retterath; Jennifer Nicholas; Julie Dart

This is an international clinical trial with the primary objectives of determining whether intervention with Angiotensin Converting Enzyme Inhibitors (ACEI), Statins, or a combination of both, when compared with placebo, will: (1) reduce albumin excretion as assessed by six monthly measurement of albumin/creatinine ratio (ACR) in 3 early morning urines; (2) reduce the incidence of microalbuminuria (MA) (ACR log mean > 3.5 mg/mmol (males) or > 4 mg/mmol

(females) in 2 out of 3 urines) at the end of the study period; (3) reduce the incidence of MA during the six month run out period following the completion of intervention phase.

This study will aim to recruit 500 adolescents with the following criteria: adolescents aged 11-16years; with type 1 diabetes of >1year duration; identified as being at high risk for the development of DN and CVD as predicted by albumin excretion in the upper tertile after

appropriate adjustment for age, sex, age at diagnosis and duration of disease. Recruitment closed in December 2012. It is a four-armed randomised clinical trial involving: (1) Quinapril: starting dose 5mg increased to 10mg daily after 2 weeks ,(2) Atorvastatin, 10mg daily, (3) Quinapril + Atorvastatin, (4) Placebo.

Funding Source: JDRF; BHF

AUSSI-ADDIT

Local Investigators: Tim Jones; Liz Davis

Study Staff: Julie Dart; Alison Roberts; Adam Retterath

This multi-centre study is investigating the changes in retinopathy, aortic intima media thickness (aIMT) and heart rate variability which are indicators of macrovascular disease and autonomic neuropathy respectively; which are complications of type 1 diabetes.

The study's aims are: (1)To determine whether adolescents with T1DM found to be at high risk of microalbuminuria have evidence of accelerated atherosclerosis, retinopathy and autonomic neuropathy as compared to adolescents at lower risk of microalbuminuria. (2) To determine whether ACE inhibition and or statin therapy during puberty will slow the progression of microvascular and macrovascular disease in T1DM

The study population is adolescents aged 11.0y to 16.9y, and with type 1 diabetes mellitus; screened as being at low risk or high risk for developing diabetic nephropathy and cardiovascular disease. Throughout Australia 370 adolescents deemed at high and 200 adolescents deemed at low in the Microalbuminuria Screening Study were recruited into the study. The study duration is 6 years, and includes a two year recruitment period and a 4year follow-up period. The study endpoints are changes in retinal images, aIMT and heart rate variability measures, after 4 years duration from baseline.

Funding Source: NHMRC Grant #632521

NEUROCOGNITIVE OUTCOMES OF CHILDREN WITH TYPE 1 DIABETES MELLITUS

Investigators: Tim Jones; Mike Anderson; Liz Davis

Study Staff: Kaitie McNamara; Nooshi Rath

Previous research has indicated that children with type 1 diabetes mellitus (T1DM) may experience deficits in their neurocognitive development compared with healthy children. Whilst the impact that T1DM has on the developing brain remains controversial, evidence suggests that these deficits may reflect the occurrence of episodes of severe hypoglycaemia. Previous studies have found a link between hypoglycaemia history and cognitive ability on a number of cognitive domains including verbal IQ, verbal memory short-term memory and attention. These findings are not always replicated and, as yet, there is no consensus as to how episodes of severe hypoglycaemia affect the developing brain. Our previous study however indicated that performance on tasks of executive function and fluid intelligence was significantly poorer in individuals with T1DM, and there is a suggestion of associated differences in frontal functioning as indicated by ERP (event-related potential) studies.

The main aim of the Neurocognitive Outcomes study is to conduct an analysis of children with TIDM's cognitive profile at an age in which both cognition and cortical development are still maturing (7-11 years). This will be achieved through the use of neurocognitive assessment, electroencephalogram (EEG) technology and magnetic resonance imaging (MRI) screens. We are also analysing the cognitive profile of a healthy sibling comparison group. In particular we will test the hypothesis that if there are cognitive deficits associated with T1DM, they are more likely to be found in measures of fluid intelligence and executive (frontal) functions. This study is run in collaboration with the Neurocognitive Development Unit at the School of Psychology, UWA.

Funding Source: PMH Foundation; APEG grant

Prevention

INTRANASAL INSULIN TRIAL II

Local Investigators: Liz Davis; Tim Jones

Study Staff: Alison Roberts; Vinutha Shetty; Mary Abraham; Martin de Bock; Jacqueline Curran; Adam Retterath;

The Type 1 Diabetes Prevention Trial, also known as the Intranasal Insulin Trial (INIT II), is part of a coordinated global effort to develop a vaccine

for type 1 diabetes. The trial, which began in 2006, is jointly funded by the National Health and Medical Research Council (NHMRC) and the Juvenile Diabetes Research Foundation, through the Diabetes Vaccine Development Centre.

If successful, this vaccine could prevent type 1 diabetes and the need for daily insulin injections in people at risk. Over the past 5 years, over 6,500 people have been screened in Australia. Before someone is diagnosed with diabetes, there is a period of time, often many years, when there are no symptoms, but the body's immune system has already begun attacking the insulin-producing cells in the pancreas. This time provides a potential opportunity to prevent further destruction of the beta cells and thus the onset of type 1 diabetes.

INITII is recruiting relatives of people with type 1 diabetes. Relatives have an increased risk of developing diabetes, which can be assessed by a simple blood test. Only 2% of the people tested will be considered at high risk of developing diabetes and be eligible to enter this trial. Testing for this study is free and can be done either at PMH or at the local blood collection centre.

Funding Source: NHMRC; JDRF

ORAL INSULIN TRIAL

Local Investigators: Tim Jones; Liz Davis

Study Staff: Julie Dart; Heather Roby; Adam Retterath

The TrialNet Oral Insulin Diabetes Prevention Study is being conducted internationally, to see if giving insulin by mouth (in a capsule) will delay or prevent T1DM in people at increased risk of developing diabetes.

Participants attend the hospital for an initial, a baseline (Randomization), a 3-month follow-up visit and then follow-up visits 6-monthly for the rest of the study. At each study visit, participants are asked questions about their health, activity, diet and about diabetes in their family and will also have a physical examination and blood tests. At the Baseline Visit, participants are randomly assigned to receive either active treatment with insulin capsule (7.5 mg insulin) or an inactive dummy capsule called placebo.

Funding Source: NIDDK; NIAID; NICHD; NCRR; JDRF; ADA

TYPE 2 DIABETES

Associate Clinical Prof EA Davis

Epidemiology

EPIDEMIOLOGY OF T2DM IN CHILDHOOD AND ASSOCIATED DISEASE COMPLICATIONS

Investigators: Liz Davis;

Study Staff: Rachelle Kalic; Jacqueline Curran; Aveni Haynes

This study is investigating the incidence of childhood Type 2 Diabetes in the Western Australian community, and the incidence of diabetes-related complications and related cardiovascular risk factors such as hypertension and hyperlipidaemia in that population

Funding Source: Departmental

Management

CAN EXERCISE TRAINING IMPROVE HEALTH IN YOUNG PEOPLE WITH TYPE 2 DIABETES?

Investigators: Liz Davis; Danny Green; Louise Naylor

Study Staff: Norhaida Mohd Yusuf; Nirubasini Paramalingam; Mary Abraham; Rachelle Kalic

Over the last few years, T2DM and obesity is becoming more common in young people. Individuals with T2DM and obesity often have high blood glucose, the effects of which can cause other major health problems such as heart or kidney disease. However studies have shown that we may be able to avoid the effects of constant high blood glucose by improving blood glucose control within the first few years of diagnosis. One way of improving blood glucose control is through exercise.

We are studying how exercise in young people with T2DM, and obese young people at risk of developing type 2 diabetes, affects: (1) The function of small and large blood vessel, and whether an exercise training program can improve function, (2) How well the body uses insulin, and (3) Whether exercise training can improve blood glucose control.

Funding Source: Pfizer APEC grant # WS1836718

OBESITY

Associate Clinical Prof EA Davis

The 2007-2008 Australian National Health Survey found that 25.1% of children aged 5-17 years in Western Australia are overweight or obese (ABS, 2011). The Obesity Research Team at Telethon Institute for Child Health Research together with the Department of Endocrinology and Diabetes at the Princess Margaret Hospital for Children, are researching the causes of obesity and interventions to combat obesity.

Investigators are collecting DNA and serum to investigate the genetic factors and biomarkers that are potential risk factors for weight gain in children and adolescents, the development of obesity-related complications, and protective factors against these complications. By collecting information on the development of obesity and successful interventions, investigators hope to alleviate the burden of childhood obesity

The team is also investigating physical, psychological and dietary factors contributing to sustainable weight loss and improved health in children and adolescents participating in the Department's lifestyle intervention programs, and participants in the trial of a new weight loss device.

Intervention

BIOENTERIC INTRAGASTRIC BALLOON

Investigators: Jacqueline Curran; Liz Davis; Colin Sherrington; Tim Jones

Study Staff: Rachelle Kalic; Luise Russel; Deanna Messina; Anna Tremayne

Weight loss treatments for adolescents who are overweight or obese include lifestyle changes that includes diet, exercise, parental involvement, reinforcement, stimulus control and self-monitoring as targeted interventions. These lifestyle interventions in children have found to result in a mean sustainable excess

weight loss of 8%. Pharmacotherapy has a very limited role in the treatment of adolescent obesity, compliance is often poor and drug choices are limited.

Studies of bariatric surgery highlight the potential weight loss that can be achieved in obese patients with the subsequent improved health, complication rates unfortunately remain high. In obese adolescents who fail to lose weight with lifestyle alone surgery is increasingly being considered. However there are currently no predictors to determine which adolescents will get complications from Laparoscopic Adjustable Gastric Banding or bypass surgery. Likewise there are no reliable predictors to determine which adolescents will have a good response from surgery, there is no available risk benefits data.

A less invasive option is the gastric balloon, achieving a temporary restriction of food intake in combination with lifestyle and behavioural changes the aim being to achieve long term weight loss. This has been achieved in adults with the use of a gastric balloon that floats in the stomach giving the individual the sensation of continued satiety, reducing their requirement and desire for food. While there have been large studies on the successful use of the BIB in obese adults. Only one small (n=5) retrospective study has been performed in adolescents with the use of the BIB. The purpose of this randomized clinical trial is to determine whether the use of the BIB aids weight loss in obese adolescents.

Specifically, that:

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

50 adolescent patients (male and female), age 12-17 years attending Princess Margaret Hospital (PMH) will recruited to the study.

Funding Source:: NHMRC # 634308; Pfizer APEC Grant

Translational Research

Clinical Prof TW Jones

Associate Clinical Prof EA Davis

The year 2013 saw the progress in our research from purely lab-based studies towards taking a step closer to translational research. This is especially in regards to the following areas of research into ways of improving the life of consumers with type 1 diabetes.

The areas in focus are:

1. The in clinic technology studies using sensor-augmented pump therapy, closed-loop insulin delivery systems and predictive low glucose management were aimed at reducing glycaemic excursions and hypoglycaemic events. This will be a boon to patients as hypoglycaemia negatively impacts on health and quality of life. The next milestone is to test the efficacy and safety of these systems with real life variables in the home environment.
2. We investigated the factors which could impact on guidelines provided to patients with type 1 diabetes in reducing the risk of hypoglycaemia associated with exercise. The potential management strategies that could be implemented to enable type 1 diabetes patients to exercise safely, will now be tested in free-living clinical trials.
3. The effect of varying macronutrient content of a meal on subsequent glycaemic excursions, was tested with the goal of later quantifying the insulin requirements and the pattern of insulin requirements for meals that vary in their protein and fat content, when the carbohydrate content is kept constant. This will enable reduction of post prandial glycaemic excursions and improve the management of patients with Type 1 diabetes

To help us move forward into translational research, we have initiated a consumer participation working party to evaluate the needs of patients with regards to their health care and sharing of health research information with them. At this early stage, the first step has been an evaluation of the preferred method of communication with patients and their families about the information from the clinical and research areas of our group.

CONSUMER PARTICIPATION

Study Staff: Barbara Sheil; Kaitie McNamara; Melanie Baker; Rachelle Kalic; Ray Davey; Sonia Johnson; Alison Roberts; Heather Roby; Mark Shah; Matt Cooper

Consultant: Anne McKenzie

Our overall aim is to promote the development and engagement of a wider diabetes and obesity community. Specifically, we aim:

- To increase consumer input in to research
- Input in to information and consent forms
- Consumer driven research proposals
- More effective result dissemination
- Wider knowledge about available research projects
- To increase consumer input in to clinical matters
- Input on clinic design & scheduling
- Input on camp format and structure
- Consumer driven education resources & materials
- Facilitation of opportunities for families to meet

Outcomes:

- A diabetes and obesity community
- Greater consumer satisfaction
- Positive research experiences
- Positive clinic experiences
- Increased social opportunities for families to meet and network
- Heightened partnership connections with: Diabetes WA, JDRF, DRF

Funding Source: Unfunded

Research Resource

REPOSITORIES AND DATABASES

Tim Jones; Liz Davis

TYPE 1 AND TYPE 2 DIABETES DNA BANK

Investigators: Tim Jones; Liz Davis

Study Staff: Adam Retterath

A prospective population-based diabetes register that conforms to international standards, and which stores demographic and clinical data on all patients attending the diabetes clinic at Princess Margaret Hospital. The database also records family history, in the first degree relative, of autoimmune disease and atopic disease As PMH is the only tertiary paediatric referral centre in Western Australia, the case ascertainment of this re n gister has consistently been over 99%. This complete, population-based data source is invaluable for studying the epidemiology of childhood onset diabetes in Western Australia.

Funding Source: Departmental

AUSTRALIAN CHILDHOOD DIABETES DNA REPOSITORY

Investigators: Grant Morahan; Tim Jones; Liz Davis

Study Staff: Heather Roby

Both types of diabetes tend to run in families. This means that certain genes we inherit from our parents may increase or decrease the risk of developing diabetes.

By testing DNA samples from families affected by diabetes, we can identify genes which increase the risk of this disease. Identification of diabetes genes is important as it will help us to understand better why some people become diabetic, and help researchers to develop new treatments.

The Australian Childhood Diabetes DNA Repository (ACDDR) is aiming to collect DNA samples from Australian families affected by diabetes. Families with a child with either type 1 or type 2 diabetes are invited to participate. DNA for the Repository is collected once via saliva samples. To participate, both biological parents and the child with diabetes provide about a teaspoon of saliva in a special pot that we supply and can be collected in clinic or at home.

The Repository stores samples of DNA, so that Diabetes researchers, with the approval of relevant Ethics Committees, can then apply to access this Repository rather than asking your child and you for more blood samples.

Funding Source: NHMR Enabling Grant

LONGITUDINAL TYPE 1 AND 2 DIABETES PLASMA AND SERUM REPOSITORY

Investigators: Tim Jones; Liz Davis

Study Staff: Adam Retterath

The Serum & Plasma bank was established to provide a store of samples from subjects with diabetes as well as their families. This resource will allow researchers to carry out scientific studies looking at the genetic causes for diabetes. The ultimate aim is to improve on current practice for prevention and monitoring of complications related to diabetes. Samples can only be accessed by research teams with appropriate ethics approval and sample details can only be accessed by authorised personnel.

Funding Source: Internal Funds

WESTERN AUSTRALIAN CHILDREN'S DIABETES DATABASE

Investigators: Tim Jones; Liz Davis

Study Staff: Jennifer Brooks; Madeleine Lowe; Adam Retterath; Helen Clapin; Vinutha Shetty; Nirubasini Paramalingam; Matthew Cooper

This diabetes register was established at Princess Margaret Hospital (PMH) in 1987 which stores data on all consenting patients attending the hospital's diabetes clinic. In Australia, all children diagnosed with type 1 diabetes (T1DM) are admitted to hospital at the time of diagnosis. As PMH is the only children's teaching hospital in Western Australia (WA), all children diagnosed with diabetes are seen by the diabetes department at this hospital. Since the diabetes register was set up, over 99% of children newly diagnosed with T1DM have consented to being registered in the register. This means that the register contains data on almost all children diagnosed with T1DM under the age of 15 years in WA, and can be used to accurately describe their characteristics.

A history of T1DM in the parents and siblings of children diagnosed with T1DM has been collected by the diabetes clinicians since 1992. Since 2005, this data collection has extended to include type 2 diabetes and other diseases associated with T1DM. This population based database for childhood is a valuable resource which will allow us to investigate the relationship between associated diseases may add to the understanding of their underlying mechanisms.

The data is collected using a questionnaire, either at the time of diagnosis for newly diagnosed patients, or during routine follow-up appointments, for patients attending the diabetes clinic. Data access will be restricted to relevant clinical and authorised research staff only. Consent is obtained from newly diagnosed patients or their parents prior to the collection and storage of incidence data and family history data in the diabetes register. Patient confidentiality is maintained.

Funding Source: Departmental

A DATABASE OF THE COMPLICATIONS OF OBESITY IN CHILDREN

Investigators: Liz Davis; Jacqueline Curran

Study Staff: Rachelle Kalic

Funding Source: Departmental

Study Summary:

The Obesity Database records the characteristics and medical complications of children with obesity who present to treatment at Princess Margaret Hospital, in an on-site database. The database records demographic and anthropometric data about participants in the study, as well as features of complications of obesity. Complications of obesity include an abnormal lipid profile, hypertension, glucose intolerance, fatty liver, musculoskeletal issues and obstructive sleep apnoea, among others. Analysis of this data quantifies the complications

of obesity in children who are overweight and obese, and will be used to develop guidelines for investigation and treatment.

WESTERN AUSTRALIAN DNA AND LONGITUDINAL SERUM BANK FOR WEIGHT REGULATION

Investigators: Liz Davis; Tim Jones; Jacqueline Curran;

Study Staff: Rachelle Kalic; Adam Retterath

The establishment of this resource will allow researchers in the future to carry out scientific studies which will look at the genetic causes of excessive weight gain (how excessive weight gain runs in families), and to identify biomarkers (special molecules) in blood that help predict individuals at risk of becoming overweight or at risk of developing obesity related diseases. Eventually the aim is to improve on current practice for prevention and monitoring of complications related to obesity.

The individuals that will be eligible for recruitment to the study will be overweight children their siblings and parents seen for their weight problem at Princess Margaret hospital, and families enrolled in the Growth and Development study through Institute of Child Health research.

DNA will be extracted from blood/saliva; serum & plasma from the blood samples The samples collected will be coded so that no one outside the PMH research team will be able identify who the sample belongs to.

Fractions of DNA and protein results may be provided to properly qualified researchers, with PMH ethics approval, to identify susceptibility genes and biomarker results may be provided to properly qualified researchers, with PMH ethics approval, to identify susceptibility genes and biomarkers related to obesity and its complications.

Funding Source: NHMRC Enabling Grant & Internal Funds

Staff and Students

HEAD OF DIVISION

Tim Jones MBBS, DCH, FRACP, MD

Clinical Professor, The University of Western Australia

Practitioner Fellow, National Health & Medical Research Council

Head, Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children

Faculty Member - Senior Principal Investigator, Centre for Child Health Research, Telethon Institute of Child Health

Adjunct Professor, Institute for Health & Rehabilitation Research, The University of Note Dame Australia

SENIOR TEAM LEADER

Liz Davis MBBS , FRACP, PhD

Clinical Associate Professor, University of Western Australia

Head, Diabetes and Obesity Services, Princess Margaret Hospital for Children

Associate Professor, School of Paediatrics and Child Health, The University of Western Australia

Faculty Member - Senior Principal Investigator, Telethon Institute for Child Health Research, The University of Western Australia

RESEARCH STAFF (TELETHON KIDS INSTITUTE))

Cooper, Matthew BSc, PhD candidate

Davey, Raymond PhD

Evans, Megan APD, BSc, Post-Grad Dip (Nutrition and Dietetics)

Haynes, Aveni BA(Hons), MBBChir, PhD

Kalic, Rachelle BPsych, MApp Econ candidate

Lowden-Crook, Casey BN

McNamara, Kaitie BA(Hons)

Nicholas, Jennifer BSc (Nursing), CDE, MSc (Diabetes Education), Nurse Practitioner Trainee

Paramalingam, Nirubasini HDip (Children's Nursing), Grad Cert (Diab Edu), BSc(Hons)

Retterath, Adam BSc(Hons)

Roby, Heather BSc

Sheil, Barbara PhD

Soon, Wayne BSc Hons

RESEARCH STAFF (PMH))

Dr Abraham, Mary

Dr Curran; Jacqueline

Dart, Julie; CRN

Dr de Bock, Martin

Dr George, Carly

Roberts, Alison; CRN

Dr Shetty, Vinutha

Dr Siafarikas, Aris

POSTGRADUATE STUDENTS

Cooper, Matthew- PhD candidate

Curran, Jacqueline- PhD candidate

Kalic, Rachelle – M App Econ Candidate

Nicholas, Jennifer- MSc Candidate

Shetty, Vinutha- PhD candidate

RESEARCH SUPPORT

Tina Commisso – B.Business (Marketing / Tourism Man)

THESES PASSED

Aveni Hanes: The epidemiology of childhood type 1 diabetes in Western Australia: trends and determinants - I think! Check with Liz she has copy

Awards

Dr Vinutha Shetty – RACP Trainee Research Award, 2013

Dr Mary Abraham – RACP Advance Trainee; WA, 2013

Telethon Fellowship, 2013

External Committees

INTERNATIONAL

Tim Jones. International Hypoglycemic Study Group – Member 2013

Tim Jones. APEG Australasian Children's Diabetes Network – Chair 2011

Tim Jones. JDRF Artificial Pancreas Consortium – Member 2011

Tim Jones. Medtronic Advisory Board Clinicians – Member 2011

Tim Jones. Australasian Paediatric Endocrine Council Research Grant Review Body – Chairman 2011-12.

Tim Jones. Australasian Paediatric Endocrinology Group Council - Member - 2001-2005

Tim Jones. Royal Australasian College of Physicians – Clinical Examiner - 2002,2004

Tim Jones. JDRF International - Scientific Review Committee Member - 2001- 2004

Tim Jones. JDRF Professional Advisory Panel- 2007

Liz Davis. Consensus Guidelines on Insulin resistance in children - Invited member of International committee 1998

Liz Davis. Australasian Paediatric Endocrine Group's Annual Scientific Meeting – local organiser - 1997

Liz Davis. Australasian Paediatric Endocrine Group - 2011-Member of Executive Council 2011 - 2013

Liz Davis. Australasian Paediatric Endocrine Group - 2005- Member Diabetes Database Committee – 2005

Liz Davis. Australasian Paediatric Endocrine Group – 2013 – Vice President – 2013-

NATIONAL

Tim Jones. National Diabetes Services Scheme Diabetes Expert Reference Group- Youth advisory Committee – Member 2013

Tim Jones. Diabetes Australia – development of the National Diabetes Strategy and Action Plan – National Expert Advisory Committee Member 2013.

Tim Jones. NHMRC Research Translation Faculty – Member 2012

Tim Jones. JDRF – Type 1 Diabetes Clinical Network Steering Committee 2012

Tim Jones. Type 1 Diabetes Guidelines Expert Advisory Group – Member 2011-2012.

Tim Jones. Diabetes & Endocrine Health Networks Advisory Group – Member 2011-2012

Tim Jones. Best Practice in Paediatrics Committee. Organising Committee – 2010

Tim Jones. Royal Australasian College of Physicians - Clinical Examiner 2002,2004

Tim Jones. Diabetes Australia Research Trust - Member Scientific Review Committee 2004-

Tim Jones. Australian Growth Hormone Advisory Committee Member 2000, Chairperson 2003-2005

Tim Jones. JDRF Australia, Scientific Advisory Committee – Member - 1999-2004

Tim Jones. Australian National Association of Diabetes Centres - Paediatric Representative 1999-2005

Liz Davis. APEG annual scientific Meeting – member of scientific organising committee 1998-2011

Liz Davis. Consensus Guidelines on Insulin resistance in children - Invited member of International committee 1998

Liz Davis. Australian Consensus Guidelines on Polycystic Ovary Syndrome - Invited member of national committee – 2010

Liz Davis. Australian Paediatric Endocrine Council Research Grant Review Body – Chairman – 2011 - 2012

Liz Davis. SAC Endocrinology, RACP - Member – 2010 - 2012

Liz Davis. Australian Tertiary Obesity Clinical Network - Member of Executive committee – 2009 - 2012

Liz Davis. Endocrine training and curriculum development subcommittee, APEG - Member 2009 - 2012

Liz Davis. Birth Defects Registry - Advisory member – 2004 -

Liz Davis. Royal Australian College of Physicians - Written Examination committee - 2000-2007

Liz Davis. Diabetes Research Foundation – board member 2004

Liz Davis. Brightspark Foundation (formerly Child Health Research Foundation) Board Member 2005

LOCAL

Tim Jones. New Children's Hospital WA Advisory Group – Member 2011

Tim Jones. Paediatric Medical Clinical Care Unit WA Medical Advisory Committee – Member 2011

Tim Jones. Diabetes Research Foundation of Western Australia - Member Medical Advisory Panel, 2002-

New Children's Hospital WA Advisory Group – Member 2011

Liz Davis. PMH-KEMH - Accreditation committee - 2001-02

Invited Presentations

Tim Jones. Risks of hypoglycemia in childhood Australian Diabetes Association. Investigators Research Symposium, New Mexico, 1997.

Tim Jones. International Diabetes Federation Congress, Mexico 2000.

Tim Jones. NZSSD Annual Scientific Meeting, May 2001.

Tim Jones. Risks of Hypoglycaemia in Type 1 diabetes, International Conference of Paediatric Endocrinology, Montreal, Canada July 2001

Tim Jones. New Zealand Diabetes Conference, "Challenges in managing diabetes in the young", September 2004.

Tim Jones. International Society of Paediatric & Adolescent Diabetes Congress, Singapore 2004.

Tim Jones. Growth in children born SGA, Symposium, Magdeberg Germany, June 2005.

Tim Jones. Hypoglycaemia in Early Diabetes. American Diabetes Association, Washington, USA 2006.

Tim Jones. Hypoglycemia in Children. Presented at the American Diabetes Association, Washington USA 2006.

Tim Jones. Neurocognitive Findings Do Not Provide Evidence for Upper and Lower Glucose Targets in Children. Presented at the American Diabetes Association 67th Annual Scientific Meeting, Chicago IL, June 2007.

Tim Jones. Treatment of Paediatric Diabetes. Presented at the China Paediatric Endocrinology Association Annual Meeting, Huan Gsang, 14th November 2007.

Tim Jones. Workshop. Exercise in Diabetes Children. International Society of Paediatric Endocrinology. South Africa 2008.

Tim Jones. Intensive Insulin Therapy. Lawson Wilkins Paediatric Endocrine Society/European Society for Pediatric Endocrinology, New York NY USA, September 2009.

Tim Jones. Barriers to Achieving Glycaemic Targets and Risks of Hypoglycaemia, Session A1C Targets in Pediatric Diabetes – Ideal vs Real. American Diabetes Association 70th Scientific Sessions, Florida, June 2010.

Tim Jones. Diabetes in Children (Plenary); Technology in Type 1 Diabetes Therapy; Pediatric Care (Discussions) Diabetes Asia 2010, Kuching, Malaysia Oct 2010.

Tim Jones. Insights into the Future of Glucose Management - Managing Hypoglycemia: a prospective view of GCM technologies. at 5th International Conference, Advanced Technologies & Treatments for Diabetes, Spain. Feb 2012

Tim Jones. Hypoglycaemia in Children and Adolescents. Invited Lecture. Adelaide November, 1995.

Tim Jones. Challenges and Advances. Asia Pacific Paediatric Endocrinology Workshop, Sydney, March 1996.

Tim Jones. Achieving Metabolic control in adolescent with IDDM. Invited lecture, ADS Annual Scientific Meeting, Sydney 1996

Tim Jones. Childhood Diabetes. Invited Lecture. Diabetes Australia Symposium, Sydney 1997.

Tim Jones. Hypoglycaemia, JDF Research Seminar, Perth, Australia, 1998.

Tim Jones. Hot topics in Diabetes. Annual Scientific Meeting of the Australian Paediatric Endocrine Group, 1999.

Tim Jones. Pump Therapy in Children and adolescents. Directions in Diabetes. Invited speaker, Queensland. March 2002.

Tim Jones. Hypoglycaemia in Children. Invited speaker. JDRF Seminar. Melbourne, March 2002.

Tim Jones. Management of diabetes in Children. Invited speaker. JDRF Type 1 Seminar. Adelaide, September 2002.

Tim Jones. Glucose Sensing Invited speaker. Australian Diabetes Society Annual Scientific Meeting, Adelaide, September 2002

Tim Jones. Research Advances: hypoglycemia. Invited speaker. Australian Diabetes Society Annual Scientific Meeting, Adelaide, September 2002.

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

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

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

Tim Jones. Consequences of hypoglycaemia. Presented at the Australasian Paediatric Endocrine Group Annual Meeting, Tasmania, Australia September 2006.

Tim Jones. Hypoglycaemia. Presented at the Diabetes Twenty Meeting, Melbourne, Australia 2006.

Tim Jones. Transitioning type 1 from childhood to young adult. Presented at the, Diabetes Association of Western Australia Annual General Meeting, Subiaco Oval, 25th October 2007.

Tim Jones. Effects of exercise on glucose. Australasian Paediatric Endocrine Group 2007.

Tim Jones. Paediatric Endocrine Cases. Presented at the 2008 Chemical Pathology Course. Fremantle Western Australia, February 2008.

Tim Jones. Common and Uncommon Presentations. Presented at the Continuous Professional Development GP Weekend-Great Southern GP Network. Albany, Western Australia, February 2008.

Tim Jones. Advances in Insulin Therapy. Pumps and CGMS. Presented at the 9th Annual Directions in Diabetes Regional Medical Conference, Melbourne Australia, Sebel Albert Park Hotel, 23-25 May 2008.

Tim Jones. Insulin Pump Services. Best Practice in Diabetes Centres. 2008.

Tim Jones. Exercise in Diabetes. ADEA/ADS. Melbourne 2008.

Tim Jones. Kimmelsteil meeting, Improving standards of care for children with Type 1 Diabetes. Melbourne, October 2008

Tim Jones. Prefer to Improve, Exercise and Glucose and Practical Pump Therapy, Queensland, November 2008.

Tim Jones. Advances in the Treatment of Type 1 Diabetes in Children. JDRF Symposium. Australian Paediatric Endocrinology Group Annual Scientific Meeting, November 2008.

Tim Jones. Insulin Pump Therapy. Australian Paediatric Society, 3rd Annual Insulin Pump Workshop, Newcastle, NSW. March 2009.

Tim Jones. Paediatric Endocrine Disorders and Fertility. Fertility Nurses Association of Australia, Perth, WA. October 2009.

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

Tim Jones. Intensive Insulin Therapy of Type 1 Diabetes and Hypoglycaemia. Novo Nordisk Diabetes Nurse Educators Symposium, Perth, May 2010.

Tim Jones. Lilly 11th Annual Diabetes Regional Medical Conference, Sydney, May 2010.

Tim Jones. Diabetes in Youth, Aboriginal Health Conference, Perth, July 2010.

How to Achieve tight controls without Hypoglycaemia. Australian Paediatric Society 5th Annual Diabetes Workshop Jul 2011.

Tim Jones. Exercise in Diabetes. Australian Paediatric Society 5th Annual Diabetes Workshop Jul 2011.

Tim Jones. Hypoglycaemia and Exercise in Diabetes. 9th Australian Paediatric Endocrine Group – Clinical Fellows School. Aug 2011.

Tim Jones. Assessing Glycaemic Variability: Does it Make a Difference in Paediatrics? Sanofi Diabetes Expert Forum, Melbourne, Oct 2011.

Tim Jones. Artificial Pancreas: Myth or Reality? Australian Diabetes Educators Association WA Branch Conference, Perth, May 2012.

Tim Jones. Numbers: Use of data in Diabetes Management and Clinical Research. Melbourne & Sydney, May 2012.

Tim Jones. Exercise and its prevention in Type 1 Diabetes. "Directions in Diabetes" Symposium. Sydney, May 2012.

Tim Jones. Regional Differences in Paediatric Diabetes. "Directions in Diabetes" Symposium. Sydney May 2012.

Tim Jones. Tots and Technology. NHMRC Clinical Trials Centre Master Class, 4th Update on Diabetes & Vascular Disease Sydney July 2012.

Tim Jones. Use of data in diabetes therapy. Australian Paediatric Society: Plenary Talks, July 2012.

Tim Jones. Invited Speaker: Preventing nocturnal hypoglycaemia. Australian Paediatric Society: Plenary Talks, July 2012.

Tim Jones. Hypoglycaemia prevention with predictive suspension of insulin delivery. Australian Type 1 Diabetes Clinical Research Network Meeting, Sydney, Mar 2013.

Tim Jones. Update on Diabetes in Children in transition. Rural Health West Symposium. Perth, Mar 2012.

Tim Jones. Success in the Next Steps to Prevent Hyperglycemia. ADS / ADEA Scientific Meeting. Sydney. August 2013.

Tim Jones. Getting better Glycemic Control with Vulnerable Patients. ADS / ADEA Scientific Meeting. Meet the Professor. Sydney. August 2013.

Tim Jones. Numbers – The Importance of Data Sets for Diabetes Research. Telethon Institute for Child Health Research Seminar. Perth Aug 2013.

Tim Jones. Closing the loop. 2013 Lilly Directions in Diabetes - Endocrinologist, Sydney, October, 2013.

Tim Jones. New Technologies in Diabetes Therapies. Western Australian Endocrine Weekend. November 2013.

Liz Davis. Obesity and Type 2 diabetes in adolescents, Kimberley Regional Medical Conference, 2002

Liz Davis. Obesity in Children and Adolescents, RACGP Annual Seminar, 2002

Liz Davis. Obesity – prevalence, investigations and management, Annual RACP update, May 2003

Liz Davis. Diabetes and hypoglycaemia: Australasian Association of Clinical Biochemists, May 2003

Liz Davis. Childhood overweight and obesity: Australian Pediatric Review Training Program, June 2003

Liz Davis. Management of Type 2 diabetes in Childhood, West Australian Diabetes Forum, June 2003

Liz Davis. Diabetes: What's new? Institute for Child Health Research Seminar Series, June 2003

Liz Davis. Australasian Paediatric Endocrine Group ASM, Symposium speaker: Insulin pumps in children, September 2003.

Liz Davis. Obesity - current trends: annual scientific update WA Dental Society, May 2004

Liz Davis. The neonate of the diabetic mother: WA branch of Perinatal Society of Australia and New Zealand, August 2004

Liz Davis. Development of a multisite protocol for bisphosphonate treatment of children with Chronic neurological disability, August 2004

Liz Davis. Childhood Obesity: Have Physiotherapists missed the boat? Presentation and panel discussion. APA WA Biennial State Conference, May 2005

Liz Davis. Obesity, super size me in the under 18's. Endocrine Nurses Society of Australia, September 2005

Liz Davis. Diabetes thru the ages. Australian Diabetes Educator Association State Conference-Keynote speaker, March 2006

Liz Davis. Obesity and T2DM in Children: South Metro Region Diabetes Update, Invited speaker, March 2007

Liz Davis. Obesity and T2DM in childhood: WA Annual Scientific meeting of Pharmacologists, Perth, May 2007

Liz Davis. Clinical Aspects of Childhood Obesity: Childhood Obesity: Prevention and Treatment Seminar, WA, May 2007

Liz Davis. T 2 Diabetes in Indigenous Youth. Australasian Paediatric Endocrine Group 25th Annual Scientific Meeting, Broome. October 2007

Liz Davis. Obesity and Emerging Policy: Community Health Nurses Clinical Practice Update. Invited speaker. Feb 2008

Liz Davis. European Society for Paediatric Endocrinology Conference, Turkey, 2008

International Society of Paediatric and Adolescent Diabetes Conference, Durban 2008

Liz Davis. European Association for the Study of Diabetes Conference, 2008

Australasian Paediatric Endocrine Group Annual Meeting, Canberra 2008

Liz Davis. T2DM in Youth – Management: Rural Health West Annual Conference. Invited speaker. May 2008

Liz Davis. T2DM in WA – Annual meeting of WA Diabetes Educator Association. Invited speaker,

May 2009

Liz Davis. Lawson Wilkins Paediatric Endocrine Society/European Society for Pediatric Endocrinology in New York, NY USA, September 2009 : Invited symposium speaker.

Liz Davis. Management of Diabetes Mellitus in Isolated Aboriginal Populations.

Liz Davis. Australasian Paediatric Endocrine Group Annual Meeting, Symposium speaker: Insulin Resistance Consensus Update: 2009

Liz Davis. Maturity Diabetes of The Young: Diabetes Nurse Educators Professional update meeting, Perth 2010

Liz Davis. Endocrine Society of Australia-Australasian Paediatric Endocrine Group, Liz Davis. Combined ESA-APEG orals – Diabetes (Clinical – 6 presentations). Invited Session Chair - Annual Meeting, 2011.

Liz Davis. Australian Diabetes Society ASM Symposium speaker: Clinical significance of genetics in Diabetes, 2011

Liz Davis. Novo Nordisk WA Endocrine Weekend 2012. Monogenic Diabetes – Case presentations and Clinical Relevance. Nov 2012

Liz Davis. International Diabetes Federation: World Diabetes Congress (Basic and Clinical Science Stream) Invited Speaker: Role and Impact of Exercise in Type 1 diabetes. Australia, 2013.

Liz Davis. Endocrine Society Paediatric Endocrinology, 9th Joint Meeting of Paediatric Endocrinology, Chair - Free Communication Session FC17 – Obesity, Milan, Italy. Sept 2013.

Liz Davis. The University of Western Australia & the Continuing Professional Development Program - Diabetes: Priorities, targets and the Annual Cycle of Care Seminar. Diabetes in Children – Risk Factors, Presentation and Treatment. Perth, June 2013.

ACTIVE collaborations

Prof Geoff Ambler: Children's Hospital at Westmead, NSW

Winthrop Prof Mike Anderson: School of Psychology, UWA

Prof Fergus Cameron: Royal Children's Hospital, VIC

Prof Jennifer Cooper: Women's and Children's Hospital, SA

A/Prof Andrew Cotterill; Mater Hospital, Qld

A/Prof Maria Craig: Australian Clinical Trials Network; NSW

Dr Dennis Daneman: Hospital for Sick Children, Toronto, Canada

Prof Kim Donaghue: Children's Hospital at Westmead, NSW

Prof David Dunger: Addenbrooke's Hospital, Cambridge, UK

Dr Jan Fairchild: Women's and Children's Hospital, SA

Prof Paul Fournier: School of Sports Science and Exercise Health, UWA

A/Prof Kym Geulfi: School of Sports Science and Exercise Health, UWA

Winthrop Prof Danny Green: School of Sports Science and Exercise Health, UWA

Prof Len Harrison: Royal Children's Hospital, VIC

Dr Joey Kaye: Sir Charles Gardiner Hospital, WA

Prof Bruce King: John Hunters Hospital for Children, NSW

Dr Lim Ee Mun: Clinical Biochemistry, PathWest, Sir Charles Gairdner

Prof Grant Morahan: Western Australian Institute for Medical Research

Dr David O'Neal: St Vincent's Hospital, NSW

Dr Carmen Smart: John Hunters Hospital for Children, NSW

Prof Ranjaney Thomas: Diamantina Institute, Qld

DRUG DISCOVERY

Overview

THE DRUG DISCOVERY TECHNOLOGY UNIT AND ITS COMMERCIALIZATION VEHICLE PHYLOGICA LTD.

The Drug Discovery Technology Unit (DDU) is focused on developing therapeutic approaches against intracellular disease-associated protein interaction targets. The research of the unit is funded by traditional sources such as ARC Linkage Grants and also from contracts with large pharmaceutical companies via a commercial entity named 'Phylogica' (http://www.phylogica.com) which was the first spin-off company from the Telethon Institute for Child Health Research.

Phylogica is a specialist drug discovery company, which identifies new prototype drugs for large drug company customers, It achieves this by drawing from its own huge source of billions of unique compounds from nature, the world's largest and most diverse collection (see below). These peptides are strongly protected by a portfolio of more than 12 patent families, including granted patents in the US and Europe. The peptide drug class which Phylogica controls access to is known as "Phylomers'. In the last 5 years Phylogica has done deals with multiple pharmaceutical companies around screening this novel class of peptides on their behalf (eg. Roche, Genentech, MedImmune/Astra Zeneca, Pfizer Cubist and Janssen).

PHYLOMERS: A STRUCTURALLY DIVERSE LIBRARY OF PEPTIDES DERIVED FROM PROTEIN FRAGMENTS ENCODED BY BIODIVERSE GENOMES

Phylogica's proprietary Phylomer® libraries represent a rich source of biologically active drug leads for a broad range of intracellular and extracellular disease targets. The Phylomer libraries are based on expressed protein fragments that are encoded by the genes of evolutionary diverse microbes. These microbes often exist in extreme environments such as deep sea volcanic vents and geysers. Typically, these peptides, which are known as Phylomer peptides, are comprised of 15 to 50 amino acids. The inherent diversity of the genetic sources of Phylomer peptides means that libraries contain multiple classes of subdomain and supersecondary structures across thousands of distinct structural families. Phylomer peptides can show excellent specificity and can function as high affinity disruptors of protein-protein interactions and binders of protein targets.

Since Phylomer libraries represent the most comprehensive collection of protein-based peptide structures available, this gives them a significant advantage over other peptide libraries of random amino acid composition. This feature of high structural diversity, has resulted in Phylomer® libraries successfully yielding high quality functional primary hits (pM-nM affinity), against multiple classes of intracellular and extracellular drug targets, as well as in direct phenotypic screens. Phylomer libraries have a number of advantages against a range of alternate random peptide screening technologies for biologic discovery. This leads to their versatile application in a range of distinct areas.

EXPANSION AND CHARACTERIZATION OF THE PHYLOMER LIBRARIES

Project Leader: Drs Nadia Milech with Drs Katrin Hoffmann, assisted by Rob Dewhurst, Laura Florez, Marie Scobie, Mark Anastasas.

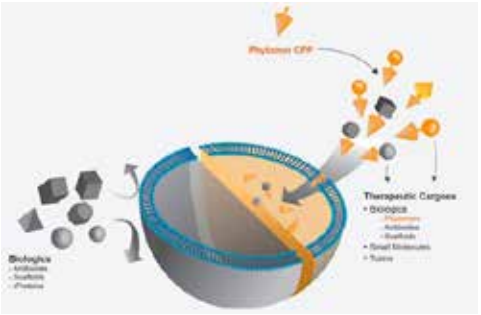
The DDU has further upgraded the complexity of its Phylomer libraries, which now comprise more than 600 billion distinct peptides across multiple display formats using the complementary M13 and T7 phages. The 14 new libraries constructed in 2013 have been made with an optimized set of microbial genomes which both span a greater diversity space. Libraries have also been constructed from a focussed set of bacterial and viral genomes from pathogenic species, which have tropisms for particular tissues. These libraries will enhance the DDU's proven capability in isolating tissue specific cell penetrating peptides corresponding to parts of natural virulence factors, which have evolved for cell invasion. In addition, the DDU has been constructing focused libraries, which are further enriched for likelihood of discovering structured drug-like peptides. More recently, the team have applied next generation sequencing approaches to assess library quality and to exhaustively interrogate the outcome of target directed screens using high various high throughput screening platforms.

Intracellular Targets and Novel Delivery Approaches

DISCOVERY AND CHARACTERISATION OF NOVEL CELL PENETRATING PHYLOMERS

Project Leader: Dr Katrin Hoffmann BSc (Hons), PhD assisted by Drs Paula Cunnigham, Nadia Milech, Suzy Jurara and Karen Kroeger as well as by Maria Kerfoot, Theresa Connor, Susan Turner, Brooke Longville, Heique Bogdawa, Mark Anastasis and Clinton Hall.

The emerging field of cell penetrating peptides (CPPs) is generating considerable excitement in the pharmaceutical industry. Not only can this class of peptide be used to deliver existing drugs inside cells but they also provide access to an entirely new landscape of intracellular targets. Indeed, estimates suggest that 80% of 'druggable' targets are located inside cells (see figure below).



CELL PENETRATING PHYLOMERS : GAINING ACCESS TO INTRACELLULAR TARGETS

Combined with the fact that CPPs can deliver new classes of drugs such as biologics into cells, one can appreciate why CPPs have the potential to significantly expand the landscape of targets

currently considered druggable.

Phylogica has screened its Phylomer libraries to identify peptides that can deliver drugs into cells. These efforts yielded 17 peptides which were confirmed as having cell penetrating activity, corresponding to a functional hit rate of 11%.

Bioinformatic analysis of these hits has identified multiple classes of novel cell penetrating Phylomers. These peptides range from the traditional short, positively charged CPPs, to novel negatively charged Phylomer peptides that mimic invasive viral peptides which are involved in cell entry and escape into the cytoplasm of the pathogens in which they evolved. We have also identified cell specific Phylomer® peptides and others that correspond to bacterial virulence factors known to be involved in cell invasion (for example: the fibronectin binding protein from Staphylococcus aureus).

ADDRESSING THE CHALLENGE OF ENDOSOMAL ENTRAPMENT

Previously we have lacked a means of directly isolating those proteins or peptides that can efficiently penetrate cells to deliver therapeutic cargoes to their targets within cells. There is significant demand for technologies that can achieve the following requirements:

- Penetrate across cell membranes (more than 80% of potential drug targets lie within this barrier which normally excludes 'smart' drugs of the biologics class).
- Target particular cells or parts of the cell (organelles).
- Ensure that once delivered into cells, drug cargos are not trapped within minute vesicles within cells (called 'endosomes'), but are instead released to be available to function to affect disease processes.

The last of these requirements presents a substantial challenge for the industry, since up to 99% of conventional cell penetrating peptides and their cargoes can remain trapped within the endosomal structures where their functionality is limited. This enormous inefficiency in delivery of protein drugs translates to very low potencies, unacceptable costs of goods and a greater potential for side effects due to escalating doses.

In 2013, the DDU developed and validated a second generation screening platform (known as the 'Endosome Escape Trap'), designed to improve significantly on the diversity and quality of cell penetrating Phylomers that can be isolated. This technology allows the specific capture of those CPP's which have escaped from the endosome to enter the cytoplasm or nucleus where their cargoes can act on targets. Some of the peptides discovered with this approach could improve intracellular delivery of a rigid protein scaffold (~10kDa) to the cytoplasm by a factor of 25-50 fold.

Intracellular Projects and Target Discovery

DEVELOPMENT OF INTRACELLULAR BIOASSAYS FOR CARGOES DELIVERED TO CYTOPLASM

Led by Dr Paula Cunningham BS. PhD assisted by Theresa Connor BSc, and Maria Kerfoot (BSc)

The group has developed two independent functional assays to monitor the efficiency with which cell penetrating peptides can deliver different therapeutic cargoes inside cells. These include:

1. a protein complementation assay for quantitation of the kinetics of CPP uptake specifically into the cytoplasm and
2. a cytotoxicity assay that measures the extent of delivery of a large toxin into the cytoplasm.

ANTICANCER PHYLOMERS: TARGETING INTRACELLULAR 'SONIC HEDGEHOG' PATHWAYS

Project Leaders: Nadia Milech BSc (Hons), PhD Head of Intracellular Projects and Target Discovery for the DDU assisted by Brooke Longville and Marie Scobie in collaboration with Julius Varano, Peter Dallas BSc (Hons), PhD and Nick Gottardo BSc (Hons) PhD FMedSci, HonDSc, (Cantab) of the Division of Children's Leukaemia and Cancer Research

Inappropriate inactivation of the 'Sonic hedgehog' (SHH) pathway causes cancer and is associated with malignancies such as basal cell carcinoma (a form of skin cancer) and a childhood brain cancer known as medulloblastoma. By targeting this pathway we aim to identify Phylomer peptides as potential anti-cancer therapeutics in these diseases. Resistance is already emerging to a small molecule drug in this area developed by Curis/Genentech. A Phylomer approach against alternative targets in this pathway may help address this resistance issue, while exploiting the encouraging efficacy seen with blockade of the SHH pathway.

Screens of Phylomers against two independent targets in the Shh pathway have yielded over 100 unique peptides. Approximately 25% of hits against each target were functionally active in an industry-standard reporter-gene bioassay we have adapted for high-throughput intracellular targeting validation. During 2013, these bioactive Phylomers were independently assessed in a cell differentiation assay, to identify the optimal lead candidates for further development. Initial results have been very promising and shown that the most effective Phylomer peptides in the reporter assay are also showing activity in the biological differentiation assay.

HIGH-THROUGHPUT PROTEIN PURIFICATION AND LIGATION CHEMISTRY

Project leader: Karen Kroeger in collaboration with Heique Bogoda, Yew Foon Tan, Scott Winslow and Mark Anasatasis.

This team have developed robust systems for the expression and purification of high Phylomer peptides and protein targets in high throughput. They have also utilized a new protein ligation technology using the Sortase A enzyme to conjugate protein cargoes such as toxins to synthetic peptides.

DISCOVERING NEW ANTIMICROBIALS AGAINST MULTI-RESISTANT MICROORGANISMS

Project Leader: Tatjana Heinrich BSc (Hons), PhD assisted by Tracy Chai.

The Drug Discovery Technology Unit has had extensive experience in the discovery of antimicrobial peptides from its phylomer libraries. Some of these peptides have activity on multiresistant isolates of *Acinetobacter baumanii*, an important cause of hospital acquired infections of burns patients. They have also screened Phylomer libraries to identify and characterize antimicrobial peptides against the related pathogen *Pseudomonas aeruginosa*, which is involved in hospital-acquired catheter and burns infections as well as lung infection, particularly in children suffering from cystic fibrosis. The group has investigated the secondary structure of antimicrobial Phylomer peptides by a technique known as circular dichroism. These studies measure the extent of formation of alpha helix structure in model membranes incorporating various phospholipid mixtures which mimicking different types of bacteria or mammalian cells. These studies found good agreement between prediction *in silico* and biophysical measurements. We also were able to optimize antimicrobial Phylomer peptides, improving the antimicrobial activity (MIC) to the high nanomolar range. In summary the DDU have identified multiple Phylomers with antimicrobial activity against the target organism *Pseudomonas aeruginosa*, as well as candidates which also have activity against clinical isolates of important nosocomial pathogens such as *Acinetobacter*, *Klebsiella* and *Staphylococcus*, while not exhibiting significant toxicity.

DISOVERY OF PHYLOMERS: WHICH INHIBIT OLIGOMERISATION OF THE BETA- AMYLOID PROTEIN

Project Leaders: Shane Stone BSc (Hons), PhD and Tatjana Heinrich BSc (Hons), PhD in collaboration with Renae Barr BSc (Hons), PhD – formerly at Edith Cowan University and now located within the DDU at the Telethon Kids Institute.

The β-amyloid protein is involved the formation of aggregates in the brain known as amyloid plaques, which are associated with Alzheimer's disease progression. Recent evidence suggests that the causative agent of Alzheimer's disease may be the more toxic oligomeric rather than the aggregated forms of the β-amyloid protein. The DDU has screened a phage display library of billions of Phylomer peptides and found several that can bind to oligomeric β-amyloid protein and also inhibit its further aggregation. These peptides are to be further analysed in functional assays by Phylogica's commercial partner Alzhyme Therapeutics.

Staff and Students

HEAD OF DIVISION

Principal Program Manager

Paul Watt BSc.(Hons) D.Phil (Oxon)

Member of Faculty, Drug Discovery Division, TICHR

Adjunct Professor, University of Western Australia

Chief Scientific Officer of Phylogica Ltd

PROGRAM MANAGER

Richard Hopkins, BSc. (Hons) PhD

Member of Faculty, Drug Discovery Division, TICHR

CEO of Phylogica

TEAM LEADERS

Paula Cunningham BSc (Hons), PhD Bioassay Development

Tatjana Heinrich BSc (Hons), PhD Phage Engineering (Macrocyclisation)

Katrin Hoffmann BSc (Hons), PhD General Phage / CPP Screening

Karen Kroeger BSc (Hons), PhD Protein Expression / Engineering

Nadia Milech BSc (Hons), PhD Intracellular Screening and Target Discovery

RESEARCH STAFF:

Mark Anastasas BSc (Hons)

Heique Bogdawa BSc, MSc, PhD

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Laura Florez BSc (Hons)

Richard Francis BSc (Hons), MSC

Suzy Juraja BSc (Hons), MSc, PhD

Maria Kerfoot BSc (Hons)

Brooke Longville BSc (Hons), PhD

Ferrer Ong BSc (Hons)

Marie Scobie BSc (Hons)

Shane Stone BSc (Hons), PhD

Yew-Foon Tan BSc (Hons), PhD

Scott Winslow BSc (Hons)

SUPPORT STAFF:

Farzana Khan BSc

Leanne Neville

Angela Purkiss

External Committees

Paul Watt BSc.(Hons) D.Phil (Oxon)

University of Western Australia, 'Pathfinder' commercialization grant panel member

Richard Hopkins, BSc. (Hons) PhD

Ausbiotech, Western Australian Committee

Invited Presentations in 2013

Paul Watt

TIDES - Oligonucleotide & Peptide, Research, Technology & Product Development 2013

TIDES 2013 12 – 15 May – Boston, USA

Chair for :

23rd American Peptide Symposium 2013

23rd American Peptide Symposium 2013 22 – 27 June – Hawaii, USA

Oligonucleotide & Peptide Based Therapeutics Summit 2013

Oligonucleotide & Peptide Based Therapeutics Summit 2013 18-19 November, 2013 – San Diego, USA

Richard Hopkins

AsiaTIDES 2013

AsiaTIDES 2013 26-27 February – Tokyo, Japan

23rd American Peptide Symposium 2013

23rd American Peptide Symposium 2013 22 – 27 June – Hawaii, USA

Next Generation Protein Therapeutics Summit 2013

Next Generation Protein Therapeutics Summit 2013 25–28 June - Coronado. CA. USA

Europhages (Phages 2013)

Europhages (Phages 2013) 10-12 September – Oxford. UK.

Ausbiotech - Australia Biotech Invest 2013

Ausbiotech - Australia Biotech Invest 2013 28-29 October – Melbourne, Australia

Active Collaborations (2013)

Professor Ashok Venkitarman, Cambridge University (Hutchison MRC Research Insititute) , Phenotypic screening and target identification

Professor Greg Weiss , University of California at Irvine CA, USA

Protein Engineering and lead optimization strategies.

Professor Kirill Alexandrov

Institute for Molecular Biosciences, University of Queensland

Dr Renae Barr

Edith Cowan University and Alzhyme Therapeutics

INFLAMMATION

Overview

Sunlight is one of the most important environmental agents to which man is exposed. The ultraviolet B (UVB) wavelengths are the most powerful and cause not only skin cancers, but also suppression of immune responses to antigens introduced at distant body sites. We have previously shown that UVB light administered to the shaved dorsal skin of mice can suppress models of allergic airways disease. In 2013, we showed that UVB light administered to the shaved dorsal skin of mice can suppress models of multiple sclerosis. This suggested that UV-induced changes in the skin could signal downstream systemic responses to allergens in respiratory tissues, and neural antigens in brain and spinal cord. In 2013, we further focussed on the effects of UV irradiation of skin on dendritic cell precursors in the bone marrow. This was important as the bone marrow produces haematopoietic cells that replace those that are dying in the peripheral organs. Erythemal UVB irradiation of skin stimulated the production from bone marrow of poorly functioning dendritic cells and macrophages (ie myeloid cells). Further, UV-induced prostanoids were responsible for the effects of UV irradiation of skin on myeloid cell precursors in the bone marrow. This result suggested that UV-induced inflammation *per se* was responsible for this effect and that it was a homeostatic response that ensured that the inflammation in the skin was restricted and did not progress out of control. We have also tested these bone marrow cells in controlling models of established inflammation. Dendritic cells generated from the bone marrow of UV-irradiated mice actively suppressed ongoing responses in antigen-sensitised mice and suggested that the dendritic cells were not only poor in function but actively regulatory. In 2013, we continued to study large numbers of chimeric mice, i.e. mice engrafted with bone marrow cells from UV-irradiated mice or mice implanted for 3 days with pellets releasing the prostanoid, prostaglandin E_2. In these chimeric mice, immune responses initiated by dendritic cells and macrophages were minimal.

In parallel studies we have investigated the effects of UV-induced vitamin D_3 in control of immune cell activity and asthma and obesity models in mice. Humans obtain 90% of their vitamin D_3 from UV irradiation of skin so it has been proposed by us, and others, that UV-induced Vitamin D_3 may contribute to the immunomodulatory effects of UV. We have examined the effect of vitamin D_3 in excess (painted onto the skin of mice with normal levels of vitamin D_3) and in deficiency (mice were fed diets restricted in vitamin D_3). We discovered that male vitamin D_3-deficient mice were unable to respond to UVB irradiation of skin for vitamin D_3 production. Thus, if the male mice responded to UVB for regulation of immunity, this was not via the modulatory properties of vitamin D_3. This finding has given us an exciting and ongoing approach to analyse the relative contribution of vitamin D_3 and other UV-induced mediators to the immunomodulatory properties of UV irradiation. We have also shown that vitamin D_3-deficient mice express worse symptoms of asthma. We have shown that vitamin D_3 and UV irradiation of skin have different effects on reducing the symptoms associated with obesity.

In 2013, we continued to analyse the impact of maternal vitamin D levels on health outcomes in children born to those mothers. The Raine cohort study has allowed studies of the impact of vitamin D in pregnancy on bone, lung and brain developmental outcomes in the children in childhood and adolescence.

Dr Jason Waithman, an NHMRC Early Career Research Fellow from the Ludwig Institute in Melbourne, joined the Inflammation Group in June 2012. He has an international reputation in dendritic cell research following his training at some of the best immunology laboratories in Melbourne. Dr Waithman has initiated several murine models of melanoma at TICHR and is studying the recognition of melanoma antigens by different immune cells. He has established sophisticated immune models by which antigens are cloned into the melanoma cells and their recognition by cells of transgenic mice under- or over-expressing receptors for that antigen analysed. Jason has initiated studies of immune recognition of melanomas in the brains of mice.

EFFECT OF UV IRRADIATION OF SKIN ON DENDRITIC CELLS GENERATED BY CULTURE FROM THE BONE MARROW

Naomi Scott, Royce Ng, Prue Hart

We have previously shown that signals sent from skin irradiated with erythemal UV to the bone marrow stimulate the development of dendritic cells that are poorly immunogenic and cannot induce a strong immune response. The phenotype and function of cells generated by culture from the bone marrow of animals administered a single inflammatory dose of UV, or multiple lower doses of UV radiation, have been studied. Different growth factors have been added to the cells in culture to generate these poorly immunogenic dendritic cells. Both GM-CSF and FMS-related tyrosine kinase 3 (Flt3-L) have been used and represent inflammatory and steady-state conditions, respectively, and stimulate different progenitor populations to differentiate. As poorly immunogenic dendritic cells are generated under all differentiative conditions, we speculate that early progenitors are altered by UV irradiation of skin. The dendritic cells generated in culture have also been able to actively down-regulate immune responses in mice already sensitised and responding to antigen. Thus, the bone marrow-derived dendritic cells from UV-irradiated mice are regulatory dendritic cells.

Funded by NHMRC, UWA Postgraduate Award to RLXN, Perron award to RLXN.

EFFECT OF UVB AND PROSTAGLANDIN E_2 ON BONE MARROW CELLS ENGRAFTED INTO CHIMERIC MICE

Royce Ng, Naomi Scott, Shelley Gorman, Prue Hart.

Regulatory dendritic cells are generated by culture of bone marrow from UV-irradiated mice. To remove the potential artificial effect of bone marrow cell culture, in 2012 and 2013 we have established several types of chimeric mice. Mice are gamma-irradiated to destroy their bone marrow cells and then injected with bone marrow cells from (a) non-irradiated or UV-irradiated mice, or (b) mice implanted with placebo pellets or pellets releasing prostaglandin E_2 (PGE_2). The re-establishment of their bone marrow was followed and by 16 weeks, the

peripheral lymph nodes have been re-populated. After 16 weeks, the efficiency of the engrafted dendritic cells has been sought as we wish to know whether the effects of the UV or PGE_2 exposure are long-lived. When an inflammatory antigen is painted on the skin of the chimeric mice, there is an inflammatory response in mice engrafted with bone marrow cells from non-irradiated or placebo-pellet-inserted mice but a very poor response if the mice were engrafted with bone marrow cells from UV-irradiated, or PGE_2-pellet-inserted mice. Responses in the airways are similarly dampened. Responses by macrophages are also reduced. These studies suggest a long lasting effect of UV irradiation, and by PGE_2 per se, on myeloid cell progenitors in the bone marrow. The effect is epigenetic as it is removed by injection of a demethylating agent. In addition, if pregnant mice are UV-irradiated, the effect of UV is measured in the bone marrow cells of the offspring.

Funded by NHMRC, UWA Postgraduate Award to RLXN, Perron award to RLXN.

EFFECT OF EXPERIMENTAL ALLERGIC AIRWAYS DISEASE ON BONE MARROW-DERIVED DENDRITIC CELLS

Naomi Scott, Royce Ng, Shelley Gorman, Prue Hart.

In response to UV-induced inflammation of the skin, bone marrow-derived dendritic cells and macrophages are regulatory. To determine whether the effect is unique to skin inflammation, the effect of inflammation at other tissue sites has been examined. In response to inflammation in the airways and in the peritoneal cavity (due to administration of the inflammasome activator, alum), bone marrow derived dendritic cells are regulatory. Further their development is blocked by the administration of indomethacin and again suggests that inflammation-induced PGE_2 is responsible. In 2012 and 2013, chimeric mice were established with bone marrow cells from mice with experimental allergic airways disease. When the chimeric mice had been engrafted for 16 weeks, the response to sensitisation and challenge with respiratory antigens was significantly reduced. When chimeric mice engrafted with bone marrow cells from mice with experimental allergic airways disease were challenged with LPS, the dendritic cells of the airways (previously labelled with a dye) were unable to migrate to the nodes and stimulate an immune response. We propose that the formation of regulatory dendritic cells in the bone marrow is part of a homeostatic mechanism to limit the destructive properties of respiratory inflammation.

Funded by NHMRC, UWA Postgraduate Award to RLXN, Perron award to RLXN

THE EFFECTS OF VITAMIN D DEFICIENCY ON INFLAMMATION AND THE MICROBIOME OF THE LUNGS

Shelley Gorman, Claire Weeden, Sian Geldnhuys, Jason Waithman, Alex Larcombe, Anthony Kicic, Prue Hart

To study the effects of early life vitamin D deficiency, we have established colonies of BALB/c mice fed a vitamin D restricted diet. The effects of gestational and neonatal vitamin D deficiency are examined by feeding female mice and their offspring a vitamin D null diet. Our published studies suggest that the severity of allergic airway disease is worse in the vitamin D-deficient mice supporting the hypothesis that vitamin D has a regulatory role in systemic immune diseases such as asthma. In addition we found that vitamin D controls asthma-inducing inflammatory cells in the lungs in a gender-specific fashion through the regulation of respiratory bacteria. In studies in 2013, we examined the lungs of naïve mice, and observed increased neutrophilia, macrophage numbers and bacteria levels in vitamin D-deficient male mice, and these effects could be reversed by vitamin D supplementation. In studies with researchers from Denmark (Dr Kenneth Barford, National Research Centre for the Working Environment; Dr Michael Roggenbuck, University of Copenhagan) we are currently investigating how vitamin D deficiency may affect the type of bacterial species that compose the microbiome of the lungs. In ongoing studies, we are examining whether changes to the structure of the lung epithelium may contribute towards the increased lung microbiota and inflammation observed in vitamin D-deficient mice.

Funded by the Brightspark Foundation

ULTRAVIOLET RADIATION SUPPRESSES OBESITY AND SYMPTOMS OF METABOLIC SYNDROME INDEPENDENTLY OF VITAMIN D

Sian Geldenhuys, Prue H Hart, Raelene Endersby, Peter Jacoby, and Shelley Gorman

In Australia, 67% of adults are overweight or obese. Causes include over-consumption of sugar and fat, and insufficient physical activity. Our novel preliminary data show that chronic skin exposure to a low dose of ultraviolet radiation (UVR) attenuates the development of obesity in mice fed a high fat diet. Exposure to UVR also had beneficial effects on glucose intolerance and insulin resistance and other risk factors for the metabolic syndrome (MetS). Past studies have linked vitamin D insufficiency to an increased risk of obesity, MetS and type-2 diabetes, but recent research suggests that this is unlikely to be causal. In our studies, the effects of UV irradiation were independent of any change in vitamin D status. These results were obtained by Ms Sian Geldenhuys as part of her Honours Project (1st Class, Edith Cowan University, Human Biology), which she completed in June 2013. Ms Geldenhuys continued to work with us as a research assistant in the second half of 2013, and performed further studies to show that the UV-related effects on obesity and MetS development occurred through vitamin D-independent, nitric oxide-dependent pathways. These studies investigating a role for UVR-induced nitric oxide have resulted in exciting new collaborations with Professors Richard Weller (University of Edinburgh) and Martin Feelisch (University of Southampton). We have also developed a novel *in vivo* imaging assay to measure nitric oxide levels in the skin of mice following exposure to UVR. In ongoing studies, we are investigating possible mechanistic pathways involving immune cells like T regulatory cells that may be responsible for curbing the development of MetS in UV-irradiated mice.

Funded by the Brightspark Foundation and the Telethon Kids Institute

MECHANISMS BY WHICH VITAMIN D SUPPRESSES SKIN INFLAMMATION

Shelley Gorman, Prue Hart

Active vitamin D analogues are currently used in the clinic to treat inflammatory skin conditions like psoriasis. We have previously shown that vitamin D applied to the skin (topically) increases the ability of immune cells like regulatory T cells to suppress subsequent skin-induced inflammation. The increased suppressive ability of the regulatory T cells was induced by skin-derived dendritic cells, and required the expression of the cytokine, interleukin-2. In 2013, we continued our studies to determine how vitamin D suppresses the development of atopic dermatitis induced by the contact sensitiser, di-nitrofluorobenzene. Topically-applied vitamin D suppressed the T cell-dependent phase (efferent) of this reaction, when applied up to 6 days before (but not after) the contact sensitiser. Vitamin D deficiency had the opposite effect, with enhanced ear-swelling responses observed during the efferent phase of the response. We observed increased mast cell numbers and IL-9+Foxp3+ T regulatory cells in the skin of vitamin D-treated mice, suggesting a functional link between mast cells and T regulatory cells for suppression of the contact hypersensitivity response. In ongoing studies we are examining a possible link between T regulatory cell responses in the skin and lung, which could be regulated by vitamin D. These studies highlight how skin treatment with active vitamin D analogues, or dietary vitamin D may be a useful for the suppression of allergic or inflammatory responses initiated in the skin.

Funded by the Brightspark Foundation

CROSS-PRESENTATION OF CUTANEOUS MELANOMA-DERIVED ANTIGENS

E Seppanen, B Wylie, J Waithman

Harnessing the immune system to treat melanoma is now a clinical reality. This approach relies on improving the ability of $CD8^+$ T cells to destroy tumours. It is well documented that tumour-specific $CD8^+$ T cells can be recovered from the blood, lymphoid organs and tumours of cancer patients. It has previously been demonstrated that robust activation of $CD8^+$ T cells occurs in the tumour draining lymph nodes. This process is considered to be dependent on cross-presentation by antigen presenting cells, such as dendritic cells. To date, the precise molecular mechanisms of this process are ill defined and controversial, but it appears that distinct dendritic cells subpopulations are attributed with this unique function. Few studies exist that provide in depth analysis of dendritic cell immunosurveillance during melanoma development and progression; even though cross-presentation is considered an extremely important event in tumour surveillance. We are identifying and characterized the dendritic cells capable of cross-presenting cutaneous melanoma antigens. An enhanced understanding of this process may provide insight into new strategies to further improve CD8+ T cell responses targeted against melanoma.

Funded by NHMRC, Cancer Australia, Cure Cancer Australia Foundation and UWA Postgraduate Award to BW

IDENTIFICATION OF THE CELL TYPES INVOLVED IN MHC CLASS II PRESENTATION OF CUTANEOUS MELANOMA-DERIVED ANTIGENS AND CHARACTERIZATION OF THE ENSUING T CELL RESPONSE

B Wylie, J Waithman

The role of $CD4^+$ T cells in anti-melanoma remains controversial and poorly understood. This lack of clarity is due to multiple factors that include the models used to interrogate their response and the complexity of their biology. Upon antigen recognition, $CD4^+$ T cells can differentiate into diverse subsets defined by a specific phenotype. Although this plasticity is well documented, the historic description focuses on their role as a helper cell in enhancing and sustaining the “more important” $CD8^+$ T cell response, which eliminate cancer by direct cytotoxicity. While this help is still extremely important, recent studies show that $CD4^+$ T helper cells can mediate tumor regression on their own and such cells are termed cytolytic CD4+ T cells. Thus, $CD4^+$ T cells can orchestrate a comprehensive immunosurveillance program that can protect and treat individuals with cancer. It has been shown that distinct dendritic cell subpopulations have the potential to drive specific specialized $CD4^+$ T cell responses. We intend to describe which subtypes are involved in MHC II presentation during melanoma progression and elucidate whether individual subtypes are promoting distinct CD4+ T cell responses. We hope to find that certain dendritic cells drive a more productive response and that this knowledge provides the foundations for translational studies targeting maximal antitumour $CD4_+$ T cell responses.

Funded by NHMRC, Cancer Australia, Cure Cancer Australia Foundation and UWA Postgraduate Award to BW

DETERMINING THE EFFICACY OF TYPE I INTERFERON SUBTYPES PROMOTING IMMUNITY AGAINST MELANOMA

A Buzzai, R Zemek, V Fear, J Waithman

Multiple subtypes of type I interferons (IFNs) exist and have been attributed to diverse functions in the immune response. Among the IFNs, IFN-α2 has been most broadly evaluated clinically. In 2011, this subtype received US FDA approval for adjuvant treatment of patients with melanoma. The primary objective of our study is to specifically address the impacts of other subtypes during melanoma.

Funded by NHMRC and UWA Postgraduate Award to AB

IMMUNITY TO MELANOMA BRAIN METASTASES

R Zemek, E Seppanen, Howlett M, Endersby R, J Waithman

Up to 75% of patients suffering from metastatic malignant melanoma develop brain metastases. Current treatments for brain metastases are limited and largely ineffective. Thus, these patients have a poor prognosis and brain metastases are the direct cause of death in 60-70% of affected patients. While immunotherapy against melanoma is now in routine clinical use, including in patients with brain metastases, very little is known about the following in the

context of melanoma brain metastases: How is intracerebral immunity coordinated? Do standard clinical treatments affect immunity at the metastatic site? This project begins to answer these questions and will improve our current understanding of immunity to melanoma brain metastases, providing insight for the design of better treatment strategies against this disease and potentially other cancers involving the central nervous system.

Funded by NHMRC and Cancer Council Western Australia

RECRUITMENT OF ENDOGENOUS ANTI-MELANOMA LYMPHOCYTES

E Seppanen, Foley B, J Waithman

Immunotherapy harnessing cytotoxic T cells achieves remissions in metastatic melanoma patients, but often tumours relapse. Successful outcomes are apparent, but it is still not known why immunotherapies are beneficial in only a percentage of patients. To improve patient outcomes it is imperative to understand the mechanisms that result in effective immunotherapy. The majority of candidate therapies entering clinical trials are single agents that target individual steps in the host anti-tumour response. Intuitively, it is hoped these agents will bolster endogenous effector T cell responses specific to multiple tumour-associated antigens. This broadened effector response, termed “epitope spreading”, is clinically correlated to enhanced survival. It is not understood how this process occurs during immunotherapy. In addition, factors that promote this response have not been explored thoroughly in a tumour setting. We aim to address how epitope spreading occurs. In addition, we aim to identify important co-factors that promote this response and ultimately enhance tumour control.

Funded by NHMRC and Cancer Council Western Australia

THE ROLE OF TISSUE-RESIDENT MEMORY T CELLS IN CUTANEOUS MELANOMA

S Winter, Endersby R, T Gebhardt, J Waithman

Until recently, it has been widely accepted that memory T cells are a heterogeneous population, comprised of two subsets: central memory (T_{CM}) and effector memory (T_{EM}) CD8 T cells. T_{CM} cells circulate within secondary lymphoid organs, where they lack immediate effector function, instead having the capability to proliferate and differentiate into cytotoxic T cells. T_{EM} cells are excluded from the lymph nodes and unlike T_{CM} cells, have immediate effector functions. Recently, a third subset of memory T cells has been recognised, known as tissue-resident memory T cells (T_{RM}). T_{RM} cells are found primarily at barrier sites including skin, gut, lungs and genital tracts, as well as the brain where they provide superior protection against local viral challenge. Research on TRM cells has mainly centred on their role in viral infections. It has been observed that post-viral infection; the T_{RM} subset remains resident at the site of pathogen entry, where they can efficiently control secondary challenge. For example, T_{RM} cells have demonstrated the ability to confer immediate protection in the skin of herpes simplex virus infected mice when presented with viral re-challenge. We are investigating whether these T_{RM} cells are present after tumour clearance or remission and if they are of a similar phenotype to those observed in viral infections.

Funded by NHMRC

Staff and Students

RESEARCH STAFF

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

Jason Waithman BSc (Hons) PhD

Shelley Gorman BSc (Hons) PhD

Naomi M Scott BSc (Hons), PhD

Elke Seppanen BSc (Hons) PhD

Sian Geldenhuys BSc (Hons)

Samantha Winter BSc

POSTGRADUATE STUDENTS

Royce LX Ng BSc (Hons), PhD Candidate, PhD awarded 2013

Ben Wylie (Hons), PhD candidate

Rachel Foong BSc (Hons), PhD Candidate

HONOURS STUDENTS

Sian Geldenhuys BSc

Rachel Zemek BSc

Sarah Lacey BSc

THESES PASSED

Royce Ng, PhD September 2012 (UWA)

Sian Geldenhuys BSc (ECU), Honours June 2013 (ECU)

Rachael Zemek, Honours December 2013 (UWA)

Sarah Lacey, Honours December 2013 (UWA)

Awards

Shelley Gorman:

Brightspark Research Fellowship 2011-1013.

Institute Small Grant, Telethon Kids Institute (2013)

National Health and Medical Research Council Project Grant (2013-2015: Zosky, Henry, Gorman, LeCras; $618,108, The link between vitamin D deficiency and chronic lung disease is due to increased airway smooth muscle, #1042235).

Jason Waithman:

NHMRC Career Development Fellowship (2014-17)

Cancer Australia and Cure Cancer Australia Grants

Elke Seppanen:

Cancer Council Western Australia Early Postdoctoral Grant

INVITED PRESENTATIONS

Prue Hart:

May: Invited symposium speaker, Australasian Society for Dermatology Research Annual Conference, Sydney. UV irradiation of skin alters dendritic cell progenitors in the bone marrow

May: Invited symposium speaker, Australian Rheumatology Association Annual Scientific Conference, Perth. Sunlight, vitamin D and autoimmunity

June: Invited seminar, Curtin University. Sunlight, vitamin D and autoimmunity

June: Invited seminar, IIID, Murdoch University. Sunlight, vitamin D, multiple sclerosis and autoimmunity

August: Invited speaker, QIMR, Brisbane. Institute Seminar Series. Sunlight, vitamin D, and autoimmunity

September: European Society for Photobiology 15th Congress, Belgium, Invited speaker in 2 separate symposia,

Symposium 1: Sunlight, vitamin D, and immunity, and

Symposium 2: Bone marrow involvement in UV-induced immunosuppression

October: Invited breakfast speaker to health professionals, Arthritis and Osteoporosis Week, Perth. Vitamin D, Hype and Immunity

November - Asia Oceania Conference on Photobiology, Sydney, invited Symposium speaker. UVR via prostaglandin E2 imprints a long-lasting effect on myeloid cell progenitors in the bone marrow

Shelley Gorman:

The National Youth Science Forum (Perth, January 2013). Your life – your contribution.

Mini-Symposium on Microbiome-DOHaD Interactions (Perth, February 2013).
Effects of vitamin D and other exogenous immunomodulators and antimicrobials on the microbiome.

School of Pathology and Laboratory Medicine, Seminar Series Royal Perth Hospital (Perth, April 2013). Skin-specific effects of vitamin D on immunity.

Murdoch Children's Research Institute, Molecular Medicine Seminar (Melbourne, June 2013). More than just vitamin D? Investigating the effects of sunlight-derived ultraviolet radiation on immunity.

Jason Waithman:

Perth Immunology Group, Perth (2013: Australia)

WAIMR Melanoma Meeting, Perth (2013: Australia)

National Young Cancer Researcher's Symposium, Melbourne (2013: Australia)

Peter MacCallum Cancer Centre, Melbourne (2013: Australia)

Murdoch University, Perth (2013: Australia)

Poster Presentation, Australasian Society for Dermatology Research Conference, Sydney (2013: Australia)

Poster Presentation, Cancer Research Institute Symposium, New York (2013: USA)

Poster Presentation, Keystone Symposia, Colorado (2013: USA)

EXTERNAL COMMITTEES.

Prue Hart:

Invited Member, NHMRC Academy

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

Member, Organising Committee, Australasian Society for Dermatology Research Annual conference, Sydney, May 2013.

Shelley Gorman:

Molecular and Experimental Pathology Society of Australia (Hon. Secretary)

LUNG GROWTH AND RESPIRATORY ENVIRONMENTAL HEALTH

Overview

We have three major research themes 1) early life determinants of lung growth, 2) respiratory environmental health and 3) mechanisms of airway dysfunction in asthma. These research themes overlap in several areas and underpin our overall goal to understand the early life factors that contribute to respiratory disease. These factors include environmental exposures, viral infection, allergic sensitization, nutritional deficiencies and genetic variability in innate lung function responses. It is becoming increasingly clear that early life exposures make a substantial contribution to respiratory morbidity and by understanding key lung development processes we aim to design interventions that will ultimately prevent the onset of respiratory disease and improve lung health in the community.

This research relies heavily on mouse models and the state of the art techniques for assessing lung function and structure that have been developed in our laboratory through ongoing collaborations with Prof Zoltan Hantos (University of Szeged, Hungary) and Prof Peter Sly (University of Queensland). These studies involve a multi-disciplinary approach whereby epidemiological and clinical studies inform the design of mechanistic animal studies; which are in turn used to identify issues that require further investigation in terms of clinical outcomes and public health. This approach is facilitated through collaborations with researchers examining clinical outcomes (Collaborators: A/Prof Graham Hall, TICHR; Prof Steve Stick, PMH; Prof Peter Sly, UQ, Prof Barry Marshall, UWA) and environmental exposure studies (Collaborators: A/Prof Merci Kusel, TICHR; A/Prof Angus Cook, UWA; Dr Andrea Hinwood, ECU; A/Prof Ben Mullins, Curtin). We also combine our measures of lung function with structural (stereology and *in vivo* imaging) and genetic studies (Collaborators: Dr Anthony Bosco, TICHR; Dr Kim Carter, TICHR) with a view to understanding critical pathways involved in lung growth and development and how these may be altered by early life insults resulting in a predisposition for disease. These studies on early life factors that impact on lung growth and disease are complemented by our ongoing work examining the mechanisms of airway hyperresponsiveness in obstructive disease. These studies are largely driven by Dr Peter Noble's *in vitro* and *in vivo* (human/animal model) work which tests new concepts of airway smooth muscle physiology and how these impact airway function in health and disease (Collaborators: A/Prof Alan James, SCGH; Prof Howard Mitchell, UWA; Dr Peter McFawn, UWA; Prof David Sampson, UWA; A/Prof Robert McLaughlin, UWA). This work is further facilitated by our longstanding collaboration with A/Prof Andreas Fouras (Monash) where we have been developing the next generation of lung imaging technology which is likely to revolutionise our understanding of lung structure and function.

Early life determinants of lung growth

VITAMIN D DEFICIENCY AND LUNG GROWTH

Rachel Foong, Shelley Gorman, Prue Hart, Tim LeCras (Cincinnati) Graeme Zosky

There has been a dramatic increase in recent decades in the prevalence of vitamin D deficiency in Australia and worldwide. Vitamin D deficiency is associated with a number of diseases including, 1) the bone disorder rickets (due to the importance of vitamin D in calcium homeostasis), 2) autoimmune disorders and 3) cardiovascular disease. Recent prominent publications have also implicated vitamin D in the pathogenesis of obstructive lung diseases such as asthma and COPD. Additionally, epidemiological studies have shown a strong association between serum vitamin D levels and lung function suggesting an important link between vitamin D status and lung health. However, there had been no study showing a direct lung between vitamin D deficiency and lung growth/structure/function. In 2010 we published a study in the leading respiratory journal (American Journal of Respiratory and Critical Care Medicine) on the lung structure and function of mice raised on vitamin D deficient and replete diets. We showed for the first time that vitamin D deficiency alters lung structure resulting in significant deficits in lung function. This study received considerable public interest resulting in an international media release by the American Thoracic Society and interviews for ABC Radio National. These studies are ongoing and we now plan to identify the mechanism of vitamin D deficiency induced alterations in lung growth. This work is being pursued by Rachel Foong who began a PhD in 2011 examining the role of vitamin D deficiency airway remodelling in chronic lung disease. Rachel has shown that vitamin D deficiency causes airway hyperresponsiveness and increases airway smooth muscle mass in female mice. These are central features of many chronic lung diseases and may explain the link between vitamin D deficiency and chronic lung diseases. In 2012 and 2013 Rachel completed a series of studies investigating if vitamin D deficiency has a role in exacerbating asthma symptoms. She found that while vitamin D deficiency caused airway hyper-responsiveness in a mouse model of asthma, it did not increase airway smooth muscle mass.

Funding: NHMRC Project Grant (2013-2015).

Respiratory environmental health

ARSENIC INDUCED NON-MALIGNANT LUNG DISEASE

Kathryn Ramsey, Peter Sly (UQ), Alexander Larcombe, Graeme Zosky

The contamination of groundwater with arsenic (As) is a global health problem and it is estimated that 100's of millions of people around the world are exposed to unsafe levels of arsenic in their drinking water. Arsenic is a well recognised carcinogen and is listed by the International Agency for Research on Cancer (IARC) as a category 1 carcinogen. However, recent evidence from an exposure event in

Chile has suggested that As is linked to the development of non-malignant obstructive lung disease. In particular, *in utero* exposure to As via drinking water has been linked to increased mortality due to bronchiectasis in young adults.

In order to investigate the link between early life As exposure and the development of lung disease in later life we conducted a series of experiments using mouse models of in utero As exposure. We began pilot studies in 2008 which involved exposing pregnant mice from three strains (C57BL/6, C3H/HeARC, BALB/c) to 100 ppb (or 0 ppb as a control) via their drinking water from gestational day 8 (prior to the development of the lung buds at day 9.5) until birth. The offspring of these mice had their lung function measured at 2 weeks of age. We found that there was no difference in lung mechanics corrected for lung volume in BALB/c mice exposed to As compared to controls. In contrast C3H/HeARC mice exposed to As had significantly higher airway resistance for a given lung volume compared to controls and As exposed C57BL/6 had higher tissue damping and elastance for a given lung volume compared to controls. These experiments provided the proof of concept data required to demonstrate the potential of As to alter lung development which may explain the link between early life arsenic exposure and poor lung health in later life. We have since completed an in depth genetic analysis of lung tissue samples from these mice and found that genes related to lung branching and mucous clearance were altered by arsenic exposure. These are important findings as they provide, for the first time, a direct mechanism that may explain the association between lung disease and arsenic exposure via drinking water observed in human populations. This work was published in 2013 in two leading environmental health journals (*Environmental Health Perspectives and BMC Pharmacology and Toxicology*).

In 2012 we also completed a series of studies examine the effect of combining arsenic exposure with an additional respiratory insult using a mouse model of influenza infection. These data demonstrated that arsenic can exacerbate influenza induced inflammation and alterations in lung function. The respiratory deficits also persisted into adulthood demonstrating the importance of early life environmental and viral exposures in determining adult lung health. This work was also published in 2013 in *Environmental Health Perspectives*. Together this work formed the basis of Kathryn Ramsey's PhD which was passed in 2013.

Funding: NHMRC Project Grant (2010-2012)

REGIONAL ENVIRONMENTAL DETERMINANTS OF LUNG HEALTH

Graeme Zosky, Kara Perks, Robert Woodward (UWA), Lucia Guiterrez (UWA), Brian Devine (UWA), Fiona Maley (UWA), Angus Cook (UWA)

Exposure to high levels of geogenic (earth derived) dust in regional towns in Australia is a public health concern. This study is the first to directly assess lung responses to inhaled "real world" particles from remote and regional towns in Australia.

In 2010 we completed Phase 1 of the CRC for Asthma and Airways funded *in vivo* animal exposure studies associated with this project. In these studies adult BALB/c mice were exposed to varying (0, 10, 30, 100 µg) concentrations of PM_{10} (< 10 µm) collected from Newman and Kalgoorlie suspended in 50 µL of saline by intranasal inoculation under light anaesthesia. Mice were assessed for inflammatory responses in the lung 6, 12, 24 hrs and 7 days post inoculation. The magnitude of the influx of inflammatory cells was dependent on the dose and sample used. A significant influx of neutrophils was observed in the mice exposed to PM_{10} from both Kalgoorlie and Newman with a greater response in mice exposed to PM_{10} from the latter. In 2012 we completed Phase 2 of these studies using samples collected from across W.A. (Kalgoorlie, Tom Price, Newman, Karratha, Port Hedland) with a view to identifying the key components of the dust that have the biggest impact on lung outcomes. We found the iron (Fe), a metal that was previously thought to be innocuous, was the key driver of the adverse lung response to geogenic particles.

In 2012/2013 we extended this study to examine the interaction between exposure to geogenic dusts and the response to influenza infection. These experiments showed that there is a synergistic interaction between the response to influenza and the response to geogenic dusts. Importantly, we also found that Fe was, again, one of the key players in the adverse impacts of exposure to geogenic dust. We are now working to uncover the mechanism/s behind the impact of Fe on the lung and have begun investigating the public health implications of exposure to iron laden dust in the remote and arid regions of Australia.

Funding: CRC for Asthma, Thoracic Society of Australia and New Zealand

ENVIRONMENTAL HEALTH OF REMOTE ABORIGINAL COMMUNITIES

Holly Clifford, Graeme Zosky, Roz Walker, Glenn Pearson

There is a significant gap in health between Aboriginal and non-Aboriginal Australians. This is particularly true for respiratory health and in individuals living in remote communities. In 2011 we commenced a research program designed to assess the role of the environment, with a focus on water quality and dust exposure, in contributing to poor lung health in these communities. We have travelled to several communities of the Martu people in the eastern Pilbara as well as Bidyadanga in the Kimberley region. We have collected water and dust samples for analysis of heavy metal contamination and we have now begun expanding this program to conduct real-time monitoring of the inhalable dust with a view to estimating exposure levels in the communities. We have also begun investigating the role of iron in dust and how this contributes to the severity of the response to respiratory infection. This year, we plan to examine the relationship between iron-rich dust in the air and direct measures of lung function in Aboriginal children.

Funding: BrightSpark Foundation; Thoracic Society of Australia and New Zealand

DIESEL EXHAUST EXPOSURE AND ITS EFFECTS ON LUNG FUNCTION AND EXACERBATIONS OF AIRWAYS DISEASE

Alexander Larcombe, Ben Mullins (Curtin), Ryan-Mead Hunter (Curtin), Anthony Kicic

This ongoing project is designed to investigate the mechanisms behind air pollution (specifically diesel exhaust and woodsmoke) induced exacerbation of airways disease. In 2009 and 2010 we established a mouse model of acute diesel exhaust particle (DEP) exposure using intra-nasal instillation of DEP (ie small amounts of DEP in solution are placed on the nose of mice and inhaled). In 2011 and 2012 we combined this DEP model with our established model of influenza infection and clearly demonstrated that DEP can enhance viral replication and exacerbate influenza induced inflammation. This observation has the potential to influence how people who are hospitalized with influenza are treated and to inform public health warnings on high pollution days. These data were published in *Influenza and Other Respiratory Viruses* in 2012.

In 2011 and 2012 we established a mouse model of whole diesel exhaust exposure by exposing mice to exhaust generated by a Euro 1 diesel engine under partial load. Exhaust gases and particles were assessed prior to entering an exposure chamber containing mice. Engine load was adjusted to obtain particle concentrations of 20 or 30mg/m^3. Mice were exposed for 2 hours per day for 8 days. During exposure, oxygen levels remained at ~20% and levels of other exhaust gases remained within short term human exposure guidelines. Exposure resulted in a dose dependent inflammatory response with the greatest pulmonary inflammation and impairment in lung function occurring 24 hours after exposure to 50mg/m^3. Mice exposed to diesel exhaust in this way also exhibited impairments in blood-brain-barrier function (published in *Journal of Applied Toxicology* in 2013).

In 2013 we performed a comparative study investigating the effect of route of exposure on the respiratory consequences of diesel exhaust exposure. We exposed mice to diesel exhaust via inhalation and to identical particles in solution via instillation. Exposure via either route elicited pulmonary inflammation and changes in lung function. We identified significant differences in response between the two routes of exposure, with mice exposed via inhalation generally displaying more realistic dose-response relationships. Mice exposed via intranasal instillation responded more variably, with little influence of dose. Our results suggest that selection of the route of exposure is of critical importance in studies such as this. Further, inhalation exposure, while more methodologically difficult, resulted in responses more akin to those seen in humans.

BIODIESEL EXHAUST EXPOSURE AND RESPIRATORY HEALTH

Alexander Larcombe, Ben Mullins (Curtin), Anthony Kicic

Biodiesel is a renewable fuel made from a variety of plant or animals oils. It is often seen as a "green" or healthier alternative to finite sources of mineral diesel, however, recent studies show that biodiesel exhaust has certain physical and chemical characteristics that also make it dangerous to health. This ongoing study employs a range of *in vitro* and *in vivo* exposure studies, detailed physical and chemical assessment of exhaust characteristics and gene expression profiling to identify what characteristics make a "healthy" or "unhealthy" biodiesel and understand the mechanisms of biodiesel exhaust induced disease.

In 2012 we made and combusted our own canola biodiesel, and measured a range of physico-chemical properties of the exhaust. We found that canola biodiesel combustion produced a greater number of particles <1µm in diameter and particles with a higher surface area to volume ratio compared to mineral diesel particles. We also showed that canola biodiesel exhaust contained greater amounts of oxides of nitrogen, carbon monoxide, carbon dioxide and oxides of sulfur compared to mineral diesel. In late 2012 we also exposed human airway epithelial cell cultures to diluted exhaust generated by combusting mineral diesel, 100% canola biodiesel, 20% canola biodiesel or pure canola oil in an unmodified diesel engine under partial load. We assessed cell viability and apoptosis 24 hrs after exposure, and inflammation (IL-6, IL-8 and RANTES) 6, 12 and 24 hours after exposure. We found that, even using the same renewable oil type (canola) there were significant differences in response to different blends. In general, exposure to exhaust from B100 or B20 combustion resulted in greater inflammation and reduced viability compared to exposure to mineral diesel exhaust. Apoptosis was highest in cells exposed to mineral diesel exhaust. These data were incorporated into a manuscript currently under review.

Funding: Thoracic Society of Australia and New Zealand, Friends of the Institute.

Mechanisms of airway hyperreponsiveness in asthma

NOVEL IMAGING MODALITIES FOR THE ASSESSMENT OF REGIONAL AIRWAY CONTRICTION

Graeme Zosky, Andreas Fouras (Monash)

In 2011 we established a collaboration with researchers at Monash University who are developing novel methods for imaging the lung using highly coherent synchrotron based radiation. These studies are conducted at the third generation synchrotron in Japan and are yielding novel insights into the regional effects of bronchoconstricting agents. In 2012 we submitted a patent for a novel imaging technology and were able secure funds through an NHMRC Development Grant to establish this technique in A/Prof Fouras's lab in Melbourne.

Funding: NHMRC Development Grant (2013-2015)

VIRAL INDUCED AIRWAY HYPERRESPONSIVENESS

Alexander Larcombe, Jennifer Phan, Rachel Foong, Anthony Kicic, Steve Stick, Peter Sly, Peter Noble (KEMH), Graeme Zosky

These studies span a number of different projects and involve infecting mice with

respiratory viruses (primarily rhinovirus and influenza) at different ages and under different conditions (e.g. in the presence of other respiratory insults). In 2010 and 2011 we focused on 2 aspects; the role of neutrophil elastase in the progression of influenza induced airway hyperresponsivness (AHR) and the impact of diesel exhaust particle (DEP) exposure during acute influenza infection. In 2011 we published studies on the sexual dimorphism in response to influenza infection in mice, and in 2012 we published a methodological study on the best technique to assess lung function in mice with influenza induced respiratory disease.

In 2012 we made significant progress in our studies on how rhinovirus infection alters the development of pathogenesis of allergic airways disease. This was prompted by recent studies which show that rhinovirus (HRV) infections account for ~90% of asthma exacerbations, however our understanding of HRV-induced disease is incomplete. A recently developed mouse model of HRV, which we combined with a mouse model of allergic airways disease using house dust mite, allowed us to directly investigate the effects of HRV infection on physiological and immunological respiratory system development. We hypothesized that early life HRV infection impairs physiological and immunological lung growth and development, disrupts antigen presenting cell (APC) function and thus results in exacerbation of allergic airways disease.

In 2012 and 2013 we completed a series studies addressing the above hypothesis. We infected mice with HRV in early life (7 days old) and studied the effects of this infection on lung function, and responsiveness to methacholine in adulthood. We also superimposed a mouse model of allergic airways disease (house dust mite) onto HRV infection to assess whether early life HRV infection potentiates asthma development. We hypothesised that HRV infection would exacerbate allergic airways disease in adult mice and that early life infection plus allergic sensitization would enhance airway hyper-responsiveness (AHR) in adulthood. To test these hypotheses, BALB/c mice were inoculated with house dust mite and/or HRV before measurement of lung function and responsiveness to methacholine. We also assessed viral load, cellular inflammation and serum antibodies. The greatest effects were seen in HDM exposed mice which had altered lung mechanics, AHR and increased inflammation. There were limited effects of HRV alone, however in adult mice, additive effects of HDM and HRV contributed to neutrophilic inflammation and there was an interaction between HDM and HRV in some parameters of lung function. These data, which formed the basis of a 1st class honours project and were recently published in *PLoS One*. In neonatal mice, more macrophages were seen in mice exposed to both respiratory insults compared with either insult alone. Exacerbation of some allergic airways disease symptoms was seen due to the combination of HDM and HRV. In late 2013 we infected neonatal mice with rhinovirus and assessed APC function. These data are still be analysed.

Funding: UWA Research Development Award (2010), ARC Discovery Grant (2011-2013), NHMRC Project Grant (2012-2014)

AIRWAY SMOOTH MUSCLE AS AN INDEPENDENT PREDICTOR OF ASTHMA

Peter Noble, Alexander Larcombe, Graeme Zosky, Alan James (SCGH), Timothy LeCras (Cincinnati), Kimberley Wang

The primary airway structure/function abnormalities in asthma include increased airway smooth muscle (ASM) mass and exaggerated airway narrowing. Importantly, recent data show that ASM mass is increased early in the natural history of asthma and remains relatively constant throughout life. This argues against the conventional paradigm whereby repeated allergic inflammation drives the remodelling process. We *hypothesise* that the mechanism producing increased ASM in asthma is independent of allergic inflammation and that the combination of increased ASM mass and allergy is required to produce allergic asthma. The specific aim of the project is to combine a newly developed mouse model of increased ASM mass with an existing model of allergic airway disease to assess the relative contributions of ASM mass and allergic inflammation to the asthmatic phenotype.

This NHMRC funded project began in 2012. The first stage of the project was to have the required mouse genotypes re-derived and sent to our Perth laboratory. The mouse models were charactered by our collaborator Professor Timothy Le Cras in his Ohio (USA) based laboratory. The required mouse genotypes have now been successfully re-derived and the mouse colony established at TICHR. In 2012-2013 we exposed mice to doxycycline, which upregulates TGFalpha expression in the airways, producing ASM growth in mice that are Egr-1 deficient. We now have preliminary data in Egr-1 deficient mice exposed to doxycycline for 10 days demonstrating greater ASM mass, increased airway narrowing and lung resistance to methacholine challenge. We also found that ASM mass also correlates to baseline resistance.

Funding: NHMRC Project Grant (2012-2014)

IMPACT OF INTRAUTERINE GROWTH RESTRICTION ON AIRWAY SMOOTH MUSCLE AND THE DEVELOPMENT OF ASTHMA

Kimberley Wang, Peter Noble, Alexander Larcombe, Sandra Davidge (Alberta)

Epidemiological studies have demonstrated that growth restriction in the womb (termed intrauterine growth restriction; IUGR) is associated with respiratory disease (including asthma) in childhood and persistent chronic lung disease in adulthood. However, it is still not known why growth restriction in early life can lead to respiratory disease. Our *hypothesis* is that IUGR is associated with increased airway smooth muscle at birth and this represents an independent risk factor for the development of asthma.

In this study, we collaborated with Professor Sandra Davidge (University of Alberta) and together we have established a BALB/c mouse model of maternal hypoxia-induced IUGR. In 2013, we have determined the optimum oxygen concentration to house the pregnant dams during the period of embryonic airway development to induce IUGR on the offspring. Our preliminary data show that offspring to dams exposed to hypoxic conditions are 19% lighter at birth but displayed “catch up growth”

at 2 weeks old, which is often seen in IUGR offspring.

Staff and Students

HEAD OF GROUP (JANUARY TO SEPTEMBER)

Graeme Zosky PhD MBiostat

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Associate Professor, Centre for Child Health Research, The University of Western Australia

HEAD OF GROUP (OCTOBER TO DECEMBER)

Alexander Larcombe PhD

Associate Principal Investigator, Telethon Institute for Child Health Research

Associate Professor, Centre for Child Health Research, The University of Western Australia

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Kimberley Wang PhD

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Luke Berry BSc

Laboratory Manager, Telethon Institute for Child Health Research

Rachel Foong BSc(Hons)

Part-time Research Assistant, Telethon Institute for Child Health Research

POSTGRADUATE STUDENTS

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Kathryn Ramsey BSc(Hons) PhD Candidate

HONOURS STUDENTS

Nicole Shaw

RESEARCH SUPPORT

Ms Marina Stubbs, Administration Officer

THESES PASSED

Kathryn Ramsey (PhD)

Nicole Shaw (1st class Honours)

Awards

Alexander Larcombe - Friends of the Institute for Child Health Research - Provision of Financial Support for Researchers and Research - $2,500.

Kimberley Wang - Friends of the Institute for Child Health Research - Provision of Financial Support for Researchers and Research - $2,500.

Graeme Zosky – Australian Institute of Policy and Science W.A. Tall Poppy Award

Rachel Foong – Lung Institute of Western Australia Junior Travel Award - $1750

Rachel Foong – Convocation, the UWA Graduates Association Ken and Julie Michael Postgraduate Travel Award - $2500

Rachel Foong – American Thoracic Society International Trainee Scholarship award – USD1000

Rachel Foong - Joint European Respiratory Society-Asian Pacific Society of Respirology Sponsorship - $3000

External Committees

INTERNATIONAL

Graeme Zosky - American Thoracic Society Respiratory Structure and Function Planning Sub-Committee

NATIONAL

Graeme Zosky - (Deputy Chair) Australian Synchrotron Imaging and Medical Beamline Program Advisory Committee

Alexander Larcombe - NH&MRC Early Career Fellowships Panel

Alexander Larcombe - NH&MRC Postgraduate Scholarships Panel

Alexander Larcombe - Safe Work Australia Expert Work Health & Safety & Workers' Compensation

Panel

LOCAL

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

Rachel Foong. Thoracic Society of Australia & New Zealand (WA) Associates Committee.

Alexander Larcombe. University of Western Australia Animal Ethics Committee.

Kimberley Wang. Australian Society for Medical Research (WA) committee member.

Invited Presentations

Graeme Zosky. Woolcock Institute Seminar Series (NSW): "Vitamin D deficiency, lung development and chronic lung disease"

Graeme Zosky. Keynote Speaker, Asthma Foundation (W.A.) Research Grant Awards: "The importance of research: towards improved outcomes for asthmatics.

Kimberley Wang. ASMR Annual General Meeting, Ballarat. "The role of Akt and microRNA signalling in cardiovascular adaptations to low birth weight".

Alexander Larcombe. Curtin University, Fluid Dynamics Research Group. "Measuring Lung Function & Growth in Mouse Models of Environmental Exposures".

ACTIVE collaborations

Assoc Prof Angus Cook, University of Western Australia

Prof Alan James, Sir Charles Gairdner Hospital, WA

Prof Zoltan Hantos, University of Szeged, Hungary

Prof Peter Sly, University of Queensland, QLD

Prof Steve Stick / Dr Anthony Kicic, Princess Margaret Hospital, WA

Dr Andrea Hinwood, Edith Cowan University, WA

Assoc Prof Andreas Fouras (Monash)

Professor Stuart Hooper (Monash)

Assoc Prof Ben Mullins / Dr Ryan Mead-Hunter, Curtin University, WA

Dr Alma Fulurija / Prof Barry Marshall, University of Western Australia

Professor John Mamo, ATN Centre for Metabolic Fitness, Curtin University, WA

Assoc Prof Timothy LeCras, Cincinnati Children's Hospital, USA

Professor Sandra Davidge, University of Alberta, Canada

Professor Peter Henry, University of Western Australia

TKI TELETHON KIDS INSTITUTE ANNUAL REPORT 2013

MOLECULAR PAEDIATRICS

Overview

The Division has continued applying its molecular expertise to the increasingly recognised importance of common respiratory infections in asthma and allergy while continuing aspects of its front line research on cat and house dust mite allergy. With the School of Paediatrics and Child Health Research (SPACH) based within our Division we have a key interest in the mechanisms involved in acute respiratory virus infections in early life, and how these affect the immune system, airway microbiome and the later development of asthma. The other key research interests of the Asthma Genetics research team (SPACH) include the epigenetics and immunogenetics of asthma, allergy, HIV (Gates grant - Africa), and early respiratory infections.

There have been many highlights including our studies measuring immunity to rhinovirus, and further evidence from our hospital admission data that continues to show the importance of human rhinovirus species C (HRV-C) in asthma. Rhinovirus is found in around 85% of children who are admitted to the emergency department at Princess Margaret Hospital with an asthma attack, and a newly-discovered type of rhinovirus (HRV-C) was associated with more severe asthma (as previously outlined in Bizzintino *et al*. ERJ 2011). Our group was the first to measure immunity to all three rhinovirus species (HRV-A, HRV-B and HRV-C) and found asthmatic children have a heightened immune response to HRV-A and B. In contrast all children had low responses to HRV-C showing marked differences between infections with the different rhinovirus species (Iwasaki *et al*. JACI, 2014). We have also recently shown that children who have had acute asthma caused by HRV-C are more likely to have a further hospital admission than children whose asthma was caused by another HRV species or another virus (Cox *et al*. AJRCCM 2013). Most interesting of all, our latest analysis shows that children with acute asthma caused by HRV-C infection have significant increases in serum IgE levels (both total and specific) during the acute attack (manuscript in preparation).

Asthma and allergy

RHINOVIRUS INFECTION IN ASTHMA AND ALLERGY

Jua Iwasaki, Wendy-Anne Smith, Siew-Kim Khoo, Joelene Bizzintino, Guicheng Zhang, Des Cox, Ingrid Laing, Peter Le Souëf, Wayne R Thomas, Belinda J Hales

Antibody levels to the three species of rhinovirus have been measured as epidemiological markers for the history of infection in asthmatic and healthy children and for immunological markers that can be used to investigate the reasons behind the known susceptibility of asthmatics to rhinovirus infection and the high coincidence of rhinovirus infection and asthma attacks. They showed heightened immunity in asthmatic children to two of the species (HRV-A and HRV-B) possibly due to increased infection or immunological over-reaction and revealed a very different type of immune response of all children to rhinovirus C, the species most associated with hospitalization from asthma. The antibodies therefore provide accurately measurable markers for further investigations that are highly relevant to asthma and the differences between infections with the different rhinovirus species.

NHMRC funded project (NHMRC Program Grant reserves ID 458 513)

ECHOVIRUS INFECTION IN ASTHMA AND ALLERGY

Jua Iwasaki, Wendy-Anne Smith, Siew-Kim Khoo, Guicheng Zhang, Ingrid Laing, Peter N Le Souëf, Wayne R Thomas, Belinda J Hales

Antibody levels to the common gastro virus, echovirus 30 were measured to compare with the distinctive anti-rhinovirus antibody pattern found in asthmatics (Project 1: Rhinovirus infection in asthma and allergy). In contrast to rhinovirus that is usually associated with respiratory infection, the anti-echovirus antibody was reduced in asthmatic children. This is in keeping with studies showing a reduced diversity of bacteria in asthmatic alimentary system and the general concept that early interactions of the immunological system of the gut with infections can profoundly shape the entire body's immune system. The antibodies accordingly provide accurately measurable markers for further investigations with echovirus and point to similar elaboration with antibodies to other gastro viruses and bacteria that infect infants.

NHMRC funded project (NHMRC Program Grant reserves ID 458 513)

INVESTIGATION INTO HOST SUSCEPTIBILITY AND IMMUNE RESPONSES IN YOUNG CHILDREN WITH ACUTE WHEEZING DUE TO HUMAN RHINOVIRUS GROUP C INFECTION

Joelene Bizzintino, Siew-Kim Khoo, Kimberly Franks, Steve Oo, Franciska Prastanti, Des Cox, Belinda Hales, Guicheng Zhang, Anthony Bosco, Ingrid Laing, Peter Le Souëf with Gary Geelhoed, David Smith, Andrew Currie, William Cookson and James Gern

In recent years, human rhinovirus (HRV) infection, particulary the newly-identified HRV group C (HRV-C), has been recognised as the cause of the majority of acute wheezing episodes in young children. Considerable evidence suggests that HRV-C is more pathogenic in this age group than other HRV groups and viruses.

Our main hypothesis is young children who develop severe wheezing with HRV-C infection have significant impairment of crucial components of their innate and adaptive immune responses to HRV-C and have adverse short and long-term responses to HRV-C infection. Specifically children who develop acute wheezing due to HRV-C have: (1) Impairment of the interferon (IFN) response to HRV-C, as evidenced by a reduction in upregulation of IFN-related gene networks that are connected by IRF7. (2) Impaired ability to generate effective antibodies to HRV-C (3) Disruption to their airway microbiome. (4) A distinctive clinical pattern of recurrent infections and wheezing episodes due to HRV-C. We aim to recruit young children (0-5 years old) presenting to the ED with acute respiratory infection to focus on IRF7-related gene network patterns in response to respiratory virus infection, antibody measurements to HRV (completed as outlined in Project 1), the genetic analysis of immunological

data, and identifying changes to the respiratory microbiome following infection with HRV-C.

NHMRC Project grant funded project (APP1045760)

DOES HUMAN RHINOVIRUS SPECIES C (HRV-C) SUPPRESS ADAPTIVE IMMUNE RESPONSES TO RESPIRATORY BACTERIA AND OTHER RHINOVIRUSES IN ASTHMATIC CHILDREN?

Cibele Gaido, Guicheng Zhang, Peter Le Souëf, Belinda Hales

We recently made the unexpected and striking discovery that a newly-discovered viral species, human rhinovirus species C (HRV-C), is not only the most common cause of asthma attacks in children admitted to hospital, but also causes more severe attacks than other viruses. We hypothesised that infection with the HRV-C species could increase susceptibility to other important bacterial pathogens. To test this hypothesis, we determined whether anti-HRV and anti-bacterial adaptive immune responses are impaired in children admitted to hospital with asthma exacerbations due to HRV-C compared with other viruses. The measurements have been undertaken and are currently being analysed.

PMH Foundation Project Grant 2013 and NHMRC funded project (APP1045760)

MOLECULARLY DEFINED IMMUNITY TO INDOOR ALLERGENS AND ASTHMA

Belinda Hales, Wendy-Anne Smith, Wayne Thomas with Susanne Vrtala, Rudolf Valenta, Marianne van Hage, William Kwok, Mark Larche

Investigations into the immune responses associated with allergic disease caused by exposure to house dust mites and cats were continued to firstly complete an appraisal of molecular nature and diversity of allergenic substances produced by the cat and secondly to provide house dust mite allergens for similar studies to be conducted with house dust mite allergy in Europe. The cat studies, which for first time compared responses to different purified cat allergens, showed that substances in the saliva including those with a molecular structure of lipocalin family were likely to more important in disease than previously assumed. Indeed combining the results with studies elsewhere it is likely that cat lipocalin-type allergens are the causes of very severe asthma found in children with allergy to multiple companion animals. Studies with the house dust mite have largely confirmed the relative importance of the different allergens previously defined by studies in Western Australia but have also been instrumental in defining the likely high importance of a newly identified allergen from the molecular family of chitin-binding proteins.

NHMRC funded project (NHMRC Program Grant reserves ID 458 513)

ALLERGIC SYMPTOMS AND IMMUNE RESPONSES OF CHINESE IMMIGRANTS IN A WESTERN ENVIRONMENT

Aarti Saiganesh, En Nee Shultz, Yuchun Li, Zhang Xiaopeng, Belinda Hales, Peter Le Souëf, Guicheng Zhang with Jack Goldblatt, Phil Stumbles and Colin Binns

Prevalence patterns for asthma and allergy have consistently been found to be significantly higher in Western countries, including Australia, than in developing countries, including China, and to be higher in urban than in farming/rural areas. These different prevalences cannot be explained by genetic dissimilarity between ancestral populations or rapid genetic changes. Environmental factors such as indoor pollutants and dietary pattern changes, through their influences on epigenetic regulation, have been proposed to be responsible for this disproportionate prevalence of allergic conditions. Understanding the basis of change in immune responses in Chinese immigrants may significantly advance our understanding of mechanisms involved in the

perpetuation of allergic diseases, specifically asthma. We investigated the immune responses and allergic symptoms in Chinese immigrants. Findings from this study can assist in understanding the complex mechanisms underlying the development of allergies and asthma in high-risk environments and populations.

Supported by the Telethon-New Children's Hospital Research Fund and NHMRC

ARE ENDOTOXIN AND HOUSE DUST MITE (HDM) ALLERGENS LEVELS RESPONSIBLE FOR DEVELOPMENT OF ALLERGIC DISEASES IN THE PEEL REGION?

Hasmita Patel, Emilija Filipovska-Naumovska, En Nee Shultz, Belinda Hales, Guicheng Zhang with Jack Goldblatt, Phil Stumbles

Asthma and atopy are "complex" heritable conditions. However, these conditions may never develop without exposure to environmental stimuli that interact with their corresponding pathway genes. Despite LPS pathway genes and environmental exposures to endotoxin and house dust mite (HDM) allergen having been individually associated with susceptibility to asthma and atopy, little is known about the interactions between them in the pathogenesis of these disorders. Thus, prevention strategies including HDM allergen avoidance and use of probiotics have so far only had a limited success. These unsuccessful interventions are likely attributable to the suboptimal understanding of the complex underlying mechanisms in the development of allergic conditions, involving interactions between genetic predisposition, timing and magnitude of different environmental factors. The study investigated the important interactions between variations of LPS pathway genes and prenatal and early exposure to endotoxin and HDM allergens with respect to the pathogenesis of allergic diseases.

NHMRC funded project

PERTH RESPIRATORY BIRTH COHORT (PRBC), PREVIOUSLY KNOWN AS THE OSBORNE PARK COHORT

Louisa Owens, Kimberley Franks, Ingrid Laing, Peter Le Souef with Dr Jack Goldblatt, Andrew Currie, Lou Landau, Catherine Hayden

The Perth Respiratory Birth Cohort (PRBC) study is one of the most prominent and comprehensive respiratory birth cohort studies to date. The cohort has many strengths including

the most extensive longitudinal assessments of respiratory function from infancy into late adolescence, the only longitudinal assessments of airway responsiveness (AR) from birth through childhood and a major analysis of immunological function in mid-childhood. It also has more detailed early pulmonary function measurements and a tightly controlled early protocol. Beginning in 1987, 253 unselected subjects were recruited before birth, studied soon after birth and followed up with comprehensive, well-characterised, face-to-face reviews on seven occasions over 24 years. To summarise, findings made on the cohort to date include establishing:

- that infant respiratory function tracks through childhood and predicts wheeze and asthma
- the pattern of airway responsiveness through childhood and the factors that influence this
- relationships between early immunological responses and immunological and respiratory outcomes through childhood
- key relationships between immune system responses, cytokine regulation and respiratory status
- the nature of age-related genetic associations with atopy and asthma

Findings to date have resulted in 63 publications, 10 book chapters, consistent international prominence and numerous invited presentations at major international scientific meetings.
The proposed study aims to extend these findings into early adulthood. Doing this will allow an examination of how early risk factors influence respiratory and immunological status in adulthood. The findings have important implications to our knowledge of whether risk factors that adversely affect children's respiratory status are the antecedents of respiratory ill health in adults.

This project was funded by the National Health and Medical Research Council and Princess Margaret Hospital Foundation Seeding Grant

RELAX

Steve Oo, Franciska Prastanti , Patrick Holt, Peter Le Souef with Peter Sly, Mimi Tang

A phase-3, multi-centre, double blind, randomised, placebo0controlled, study testing the efficacy of winter only treatment with omalizumab for the reduction of asthma exacerbations in children aged 6-15. Primary endpoint: proportion of children with acute asthma exacerbations during treatment period. Secondary: 1) The proportion of viral respiratory infections that result in lower airway symptoms during the treatment period; 2) lung function and airway responsiveness over the follow-up period. Mechanistic: 1) aeroallergen specific IgE titres over the follow-up period; 2) Allergen-specific Th2 memory responses over the follow-up period; 3) the circulating pool of FcER1+ myeloid cells; 4) gene activation signatures on circulating myeloid cells during acute exacerbation; 5) presence of virus and interactions between virus and bacteria. Safety: urticaria or anaphylaxis to omalizumab, treatment-related adverse events, haematology and clinical chemistry.

Lay summary for your project – A phase-3, clinical trial whereby the drug, omalizumab, is administered to children aged 6-15 suffering from repeat asthmatic attacks. This is to determine the effectiveness treatment of this drug for the reduction of asthmatic attacks in winter, a season when asthma exacerbations are most frequent.

This project is funded by the National Health and Medical Research Council

CYSTIC FIBROSIS GLUTATHIONE GENETICS

Ingrid Laing and AREST CF

To identify the glutathione pathway gene variations that alter lung glutathione levels and begin to elucidate the initiation of lung disease in CF. This knowledge will facilitate the identification of therapeutic intervention targets prior to the establishment of respiratory infection, with treatments targeted to those most likely to be affected and to the most relevant tissue compartment, in an effort to slow the development of respiratory OS and inflammation, reduce airway damage and delay the onset of bronchiectasis.

This project is funded by the University of Western Australia

INFECTIONS IN AFRICAN POPULATIONS

Alicia Annamalay, Siew-Kim Khoo, Belinda Hales, Ingrid Laing, Peter Le Souef with Quique Bassatt, Robin Green, Miguel Lanaspa, Salome Abbott, Andrew Currie, William Cookson, James Gern, David Smith, Jack Goldblatt

This project is comprised of case-control and cross-sectional studies from three distinct populations in Africa (Mozambique, South Africa and Morocco). The key aims of this project are to identify the viruses and bacteria associated with acute lower respiratory infections (ALRI) and to investigate the host immune responses (i.e. cytokine and antibody responses) associated with respiratory infections in young African children. The results of this project will elucidate the role of viruses, bacteria and host immunity in childhood ALRI and may therefore contribute to preventative and clinical strategies as well as lead to further biomarker discovery studies.

This Project was funded by the Lung Institute of Western Australia, Alan King Westcare Project Grant

GAMA

Erica Parker, Holly Clifford, Peter Le Souef with D Naniche, J Blanco, LLuis, Menedez C, L Pastor, E Pedro, J Pita, J Ruiz, B Sigaugque, J Langhorst,

Le Souëf's group component: Development of novel biomarkers distinguishing early HIV infection from longstanding infection in a Sub Saharan African setting.

Aims: 1) Conduct microarray for host gene expression of cytokine,chemokine and IBD GI biomarkers; 2) Analyze individual biomarkers for their mean duration of recency from the longitudinal cohort, and determine false recent rate from the longstanding HIV infected patients; 3) Analyze combinations of biomarkers for best distinguishing recent from longstanding HIV infection.

This project was funded by the Bill and Melinda Gates Foundation

GENOME-WIDE DNA METHYLATION PROFILING IN CHILDREN WITH ACUTE ASTHMA AND HRV-C INFECTION

Siew-Kim Khoo, En-nee Schultz, Joelene Bizzintino, Peter Le Souef, Patrick Holt, Guicheng Zhang with Jack Goldblatt

We recently found that human rhinovirus group C (HRV-C) was the most common viral group causing severe acute wheezing episodes, and half of the acute wheezing attacks, in young children. More importantly, we found that HRV-C was the only respiratory virus that was associated with atopy (defined by skin prick tests), total and specific IgE in an acute asthma cohort, suggesting that HRV-C may be the key to asthma exacerbations and the development of allergy and asthma in children. Our team, together with Prof Patrick Holt in Cell Biology, have investigated the gene expression profile of peripheral blood mononuclear cells (PBMC) using a genomics-based approach in the acute asthma cohort. Methylation, which is a persistent, but also reversible epigenetic code, has central epigenetic roles in cellular processes including genome regulation, gene expression and development and disease. We propose to investigate genome-wide methylation patterns of PBMC in children with acute asthma associated with HRV-C, compared to methylation profiles of the same subjects in convalescence, to children with acute asthma associated with HRV-A and in healthy children without HRV and other respiratory virus infections. The study is timely to explore an epigenetic explanation to the role of HRV-C in asthma exacerbations and the development of asthma and allergy in children. In order to cover a wider spectrum of genes in the whole genome, this proposed project will use an Illumina 450k Infinium Methylation BeadChip (Infinium Methylation 450K; Illumina, Inc. CA, USA). The Infinium 450K includes 485,577 assays (482,421 CpG sites, 3091 non-CpG sites and 65 random SNPs). The array covers a total of 21,231 genes with a global average of 17.2 sites per gene region. This study will comprehensively investigate the methylation changes in relation to infection with different HRV strains in children with acute asthma recruited at the Princess Margaret Hospital for children (PMH). Dr Zhang, the chief applicant has a solid background in both genetic and epigenetic aspects of asthma and allergy and biostatistics. He will use a gene co-expression network analysis algorithm to investigate co-methylation networks in the response to HRV-C infection in children with acute asthma. The study will increase our understanding of the mechanisms underlying asthma exacerbations and the development of allergic disorders and asthma in relation to HRV infection. The findings should facilitate designing and testing of new preventive strategies or therapeutic interventions (targeting methylation profiles) in Australia, where asthma is a significant social burden.

This project was funded by the Princess Margaret Hospital Foundation.

Staff and Students

SENIOR PRINCIPAL INVESTIGATORS

Wayne Thomas, PhD, Professor, Head of Division

Peter Le Souëf, MD, MRCP, FRACP, Head, School of Paediatrics and Child Health (SPACH), UWA: Head, Immunogenetics Research Group, SPACH, UWA

ASSOCIATE PRINCIPAL INVESTIGATORS

Belinda Hales, PhD, Associate Professor

Guicheng Zhang, PhD, Honorary Research fellow, Associate Professor (research) in SPACH

RESEARCH STAFF

Ingrid Laing, PhD

Joelene Bizzintino, PhD

En Nee Shultz, BSc (Hons)

Emilija Filipovska-Naumovska, MD, PhD

Yu Chun Li, PhD

Zhang Xiaopeng, MD

Siew-Kim Khoo, BSc (Hons)

Kimberley Franks, BSc (Hons)

Franciska Prastanti, MBBS

POSTGRADUATE STUDENTS

Jua Iwasaki, BSc (Hons), Doctor of Philosophy

Alicia Annamalay, BSc (Hons), Doctor of Philosophy

Stephen Oo, MBBS, Doctor of Philosophy

Louisa Owens, MBBS, Doctor of Philosophy

Cibele Gaido, MSc, Doctor or Philosophy

Melinda Judge, BSc, (Hons) Doctor of Philosophy

Aarti Saigenesh, BSc, Honours

Hasmita Patel, BSc, Honours

Leesa Harris, BSc, Honours

Cassie Robertson, BSc, Honours

Erica Parker, Honours

RESEARCH SUPPORT

Lea-Ann Gourlie

Marina Stubbs

THESES PASSED

Serena O'Neil, PhD, The University of Western Australia, Identification and characterisation of cat allergens

Aarti Saigenesh, Honours, The University of Western Australia, Allergic symptoms and immune responses of Chinese immigrants in a Western environment

Hasmita Patel, Honours, Murdoch University, Are endotoxin and house dust mite (HDM) allergens levels responsible for development of allergic diseases in the Peel region?

Leesa Harris Honours, The University of Western Australia, Contribution of MNDA gene variation

to wheezing attacks and response to treatment

Cassie Robertson, Honours, The University of Western Australia, Persistence and Recurrence of Human Rhinovirus Group C in children that suffer acute wheezing attacks

Erica Parker, Honours, The University of Western Australia, Acute HIV in Africa: The relationship between viral load at presentation and clinical outcomes in the early stages of disease.

Awards

Alicia Annamalay, Asthma Foundation PhD Top-up Scholarship

Alicia Annamalay, Convocation Award by UWA Postgraduate Research School

Alicia Annamalay, UWA Postgraduate Travel Award

Jua Iwasaki, Asthma Foundation PhD Top-up Scholarship

Jua Iwasaki , Friends of the Institute International Travel Award

Jua Iwasaki , European Academy of Allergy and Clinical Immunology – World Allergy Organization Travel Award

Stephen Oo, Telethon Research Fellowship Scholarship

Stephen Oo, American Thoracic Society Abstract Scholarship Award

Louisa Owens, UWA International Postgraduate Research Fellowship

External Committees

INTERNATIONAL

Wayne Thomas, Member, International Union of Immunological Societies (IUIS) Allergen Nomenclature Subcommittee

Wayne Thomas, Member, World Allergy Organization (WAO) Aeroallergens Committee

Wayne Thomas, Member, World Allergy Organization (WAO) Ask the Expert Panel

Peter Le Souëf, Member, Pediatric Advisory Board, INTERASMA.

Peter Le Souëf, WAO Special Committee on Pediatric Asthma, World Allergy Organization, Chair

NATIONAL

Peter Le Souëf, Councillor, AMA and AFWA representative

Peter Le Souëf, Australian Council on Smoking and Health, 2004–present

Invited Presentations

Wayne Thomas, Towards the prevention and therapy of allergy. SFB (Special Research Program of Austrian Science Fund) Work in progress. Invited discussant. Ottenstein, Austria (3/11/13).

Wayne Thomas, Innate Immunity to Allergens. Symposium, Asia Pacific Congress of Allergy, Asthma and Clinical Immunology. Taipei, ROC (14/11/13)

Wayne Thomas, 2013 History of Molecular Allergology, Keynote Lecture, International Symposium on Molecular Allergology, Vienna, Austria (5/12/13)

Peter Le Souëf, Overview of aerosol devices and therapy today" Workshop: State-of-the-Art in Aerosol Therapy" Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Darwin, 25 March 2013

Peter Le Souëf, "The role of respiratory viruses in children's asthma" National Forum on Pediatric Asthma and Allergy, Beijing, China, 21st April 2013

Peter Le Souëf, "Asthma control in China" National Forum on Pediatric Asthma and Allergy Beijing, China, 21st April 2013

Peter Le Souëf, "Are inhaled steroids helpful in infants with recurrent wheeze?" Symposium: Treatment and outcome of preschool wheeze, European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization, World Allergy and Asthma Congress 2013 Milan, 24 June 2013

Peter Le Souëf, "Allergy and asthma" Symposium: Year in review – asthma European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization, World Allergy and Asthma Congress 2013 Milan, 25 June 2013

Peter Le Souëf, "Virus and asthma: the starter or the main cause?" Plenary lecture, Asia Pacific Association of Pediatric Allergy, Respiratory and Immunology (APAPARI), Bangkok, 2 October 2013

Peter Le Souëf, "The science of aerosol medications" Symposium, Asia Pacific Association of Pediatric Allergy, Respiratory and Immunology (APAPARI), Bangkok, 2 October 2013

Peter Le Souëf, "Maintenance inhaled-steroids should be used in preschool wheezers?"

Con in Pro-Con Symposium, Asia Pacific Association of Pediatric Allergy, Respiratory and

Immunology (APAPARI) Bangkok, 3 October 2013

Peter Le Souëf, "The revolution in diagnostic lung imaging - changing how we practice"

Symposium II: Pulmonology, Hong Kong Society of Paediatric Respirology, Hong Kong, 6 October 2013

Peter Le Souëf, "Triggers for acute asthma – which causes what, when and why?" Plenary lecture - Symposium III Hong Kong Society of Paediatric Respirology , Hong Kong, 6 October 2013

Belinda Hales. ' The origin and health

implications of the lung microbiome'. Symposium speaker. DOHaD Micobiome Symposium, KEMH, Perth (7/2/2013).

Belinda Hales. 'Rhinovirus and the respiratory microbiome in asthma and atopy'. Invited speaker. Pathology and Laboratory Medicine Seminar Series, University of Western Australia, Perth (11/10/2013)

Guicheng Zhang, BIT's 11th Annual Congress of International Drug Discovery Science & Technology, Therapy and EXPO, Haikou, China (13-16/11/2013), Invited Speaker

ACTIVE collaborations

Mark Larche, McMaster University, Canada

William Cookson, Imperial College London, UK

James Gern, Wisconsin University, USA

John Upham, UQ, Australia

Anne Chang, Menzies; Royal Children's Hospital Brisbane, Australia

Shelley Walton, University of the Sunshine Coast, Australia

Frode Jahnsen, Oslo University, Norway

Rudolf Valenta, (Medical University of Vienna, Austria

Marianne van Hage, Karolinska Institute, Sweden

William Kwok, Benaroya Research Institute, USA

Peter Sly, UQ, Australia

Kate Holt, Bio21, University of Melbourne, Australia

Anna-Maria Dittrich, Hannover Medical University, Germany

William Pomat, The PNG Institute of Medical Research, PNG

Mimi Tang, Murdoch Children's Research Institute, Australia

Quique Bassatt, Barcelona Centre for International Health Research, Manhica Health Research Centre

Robin Green, University of Pretoria, South Africa

Miguel Lanaspa, Barcelona Centre for International Health Research, Manhica Health Research Centre

Salome Abbott, [4]University of Pretoria, South Africa

PAEDIATRIC RESPIRATORY PHYSIOLOGY

Overview

The Paediatric Respiratory Physiology research group was established in mid 2010 with the appointment of Prof Graham Hall by the Telethon Institute for Child Health Research. The primary aim of the group is the assessment of lung growth and development in both health and in respiratory disease, including asthma, cystic fibrosis and chronic lung disease of prematurity.

Cystic Fibrosis

Evolution of airway function and inflammation in early CF lung diseaseproject staff

Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Kathryn Ramsey, Caroline Gallagher and Tim Rosenow as part of the AREST CF collaboration (www.arestcf.org)

Cystic Fibrosis (CF) is a condition of chronic inflammation and infection resulting in destruction of lung architecture eventually leading to death. We and others have shown that infants and young children with CF show evidence of early inflammation and infection and reduced lung function. This highlights this period of life as a critical period for the development of new treatments to prevent progression or even reverse lung disease. However, the development of lung disease in early infancy is poorly understood and ongoing relationships between peripheral lung function and measurements of pulmonary inflammation or infection remain unknown. The goals of this study are to evaluate objective measurements of respiratory function and their combined ability to detect and monitor the presence of lung disease early in the life of infants and young children with cystic fibrosis.

This project is funded by the National Health and Medical Research Council of Australia and the USA Cystic Fibrosis Foundation

LUNG TERM OUTCOMES OF INFANT LUNG FUNCTION IN CYSTIC FIBROSIS

Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Kathryn Ramsey, Caroline Gallager and Tim Rosenow

As part of the AREST CF collaboration we have developed a unique and internationally recognised early surveillance program for the detection of lung disease in CF that includes complex measurements of lung function obtained in infants newly diagnosed with CF following newborn screening (NBS). We are the only group in the world to have comprehensively studied population-based cohorts of children diagnosed by NBS using such tests. In this project we aim to evaluate the longer term lung structural and functional outcomes associated with lung function measurements made during infancy. These data will inform the clinical importance of measuring lung function during infancy in CF and also the role of the tests in proposed early intervention studies in CF. Such data are eagerly anticipated by the global CF community. This project is funded by the National Health and Medical Research Council of Australia

VIRAL PATHOGENESIS OF EARLY CYSTIC FIBROSIS LUNG DISEASE

Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Kathryn Ramsey

Infectious insults can profoundly change the trajectory of CF lung disease. Virus infections can lead to significant morbidity, but their effect on the early origins and progression of CF pulmonary disease is ill-defined. In this project, powerful nucleic acid-based detection approaches will be used to prospectively characterize infections in infants, and determine the impact of viruses on bacterial colonization, airway inflammation, physiological measures, and structural changes, thus elucidating early pathogenic events in CF lung disease. This project is funded by the National Institutes of Health (USA) and National Health and Medical Research Council of Australia.

Indoor air pollution and lung health

IMPACT OF EXPOSURE TO AIR POLLUTANTS DURING THE PRENATAL PERIOD ON LUNG FUNCTION IN INFANCY

Graham Hall, Peter Franklin, Zoltan Hantos, Shannon Simpson, Mark Tan and Naomi Hemy with the Peel Child Health Study (www.peelchildhealthstudy.com.au)

This project aims to assess the impact of prenatal environmental exposures on lung function in infancy. In particular we wish to:

- Determine the impact of air pollution, particularly indoor air pollution, during the prenatal period on lung function in infancy.
- Investigate the different measures of infant lung function for detecting early lung changes in response to prenatal environmental exposures.
- Assess the impact of early life exposure to air pollution on respiratory symptoms during infancy

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

Long term outcomes following preterm birth

INVESTIGATION OF THE INFLUENCE PRETERM BIRTH ON LUNG STRUCTURE AND FUNCTION IN SCHOOL AGE CHILDREN

Graham Hall, Andrew Wilson, Jane Pillow, Andrew Maiorana, Shannon Simpson, Karla Logie, Chris O'Dea, Maureen Verheggen.

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of premature birth. Contemporary BPD is dominated by peripheral lung abnormalities including failed alveolarisation with a decreased number of large and simplified alveoli and abnormal pulmonary vascular development. The few studies to examine the long term respiratory outcomes in new BPD have demonstrated impaired gas transfer reduced cardiopulmonary exercise capacity, gas trapping and increased respiratory morbidity. None of these studies undertook a comprehensive assessment of lung structure, peripheral lung function and respiratory morbidity and examined the influence of neonatal history on the long term

outcomes of new BPD. Studies of this nature are essential and will provide an improved understanding of the pathology of new BPD and its long term outcomes and allow a more targeted approached to the treatment and management of infants with BPD through the neonatal period and into childhood.

Key outcomes include

All preterm children have abnormal lung structure, irrespective of the presence of BPD.

- Children with a history of BPD more likely to exhibit exercise flow limitation when compared to preterm children without BPD and healthy children.
- All pre-term children have a reduced exercise capacity, and children with BPD have an altered ventilator pattern to exercise.
- Preterm children (with and without BPD) had reduced lung function. Specifically, significant reductions in spirometry, gas trapping and altered peripheral lung mechanics.
- Respiratory Symptoms are increased in preterm children irrespective of a diagnosis of BPD. Children with respiratory symptoms in the last year had worse lung function outcomes than children without recent symptoms

This project is funded by the National Health and Medical Research Council of Australia, Raine Foundation and Princess Margaret Hospital Foundation

Congenital Diaphragmatic Hernia

LONG-TERM RESPIRATORY, CARDIOVASCULAR AND QUALITY OF LIFE OUTCOMES OF NEONATAL CONGENITAL DIAPHRAGMATIC HERNIA PATIENTS IN WESTERN AUSTRALIA

Dr Jason Tan, Dr Corrado Minutillo, Prof Graham Hall, Prof Jan Dickinson, Mrs Maureen Verheggen, Dr Jim Ramsey and Georgia Banton

Babies born with a congenital diaphragmatic hernia are at risk of significant morbidity and mortality. Acute problems generally arise from pulmonary hypoplasia or agenesis, pulmonary hypertension and surgical intervention. Long-term complications have been documented however vary between units as management options differ. There are no long-term data available for the Western Australia cohort at present. This study is a pilot study to summarize the long-term respiratory, cardiovascular, quality of life and psychological well-being outcomes in our cohort of CDH patients. The baseline information will be used to develop a framework for a follow-up program in Western Australia to improve long-term outcomes and enable future research in this area.

This project is funded by the Telethon

Asthma

RISK FACTORS FOR THE DEVELOPMENT OF LATE ONSET AND PERSISTENT ASTHMA IN YOUNG ADULTS: A LONGITUDINAL BIRTH COHORT STUDY

Investigators: Prof Graham Hall, Prof Patrick Holt, Dr Elysia Hollams, Prof Zoltan Hantos, Prof Nick de Klerk, Dr Anthony Bosco, Elisha White and the Raine study team (www.rainestudy.org.au)

Australia has one of the highest incidences of asthma in the world, with 14-16% of children and 10-12% of adults diagnosed as asthmatic. Early-life factors involved in the development of childhood asthma have been well explored however it remains largely unknown whether these risk factors, or other yet unidentified factors, are involved in the development of later onset asthma or persistence of childhood asthma into adulthood. While many children with asthma continue to have asthma as adolscents and young adult, some children grow out of their asthma, equally some people develop asthma for the first time as young adults. This study aims to examine the risk factors for the remittance and persistence of childhood asthma, as well as the development of later-onset asthma within 23 year old participants of the Raine study birth cohort. Data collection for this project is still ongoing and will be completed in mid-2014. However, we have already found some surprising findings including some that challenge the use of some asthma diagnosis tests in community groups as well as early suggestions of which risk factors are associated with asthma in the young adults.

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

MEASUREMENT OF BRONCHIAL HYPER-RESPONSIVENESS IN YOUNG CHILDREN: MANNITOL AND EXERCISE CHALLENGE TESTING

Prof Graham Hall, Dr Shannon Simpson, Prof Stephen Stick, Dr Afaf Albloushi and Ms Georgia Banton

The addition of objective measures of bronchial hyper-responsiveness (BHR) to current clinical practice may result in improved diagnosis and management of young children with exercise related symptoms. This project aims to determine the feasibility of BHR testing using the forced oscillation technique (FOT) as a primary outcome of the mannitol challenge test in pre-school children with exercise induced symptoms. In addition we aim to determine the agreement of the mannitol challenge test and exercise challenge test in these children.

We found that 85% of children aged three to seven years and 100% of children aged 4-7 years were able to complete the mannitol challenge using FOT as the outcome measure. The three children that failed to complete the test were three years of age and did not complete due to difficulty sustaining attention.

Further research comparing mannitol and exercise challenge tests and to define appropriate cut off levels to support the diagnosis of excise induced bronchoconstriction in young children is ongoing.

This project is funded by the Asthma Foundation of WA and Australian and New Zealand Society of Respiratory Science

RISK ASSESSMENT AND PREVENTION OF RESPIRATORY COMPLICATIONS IN PAEDIATRIC ANAESTHESIA

Graham Hall, Britta Regli-von Ungern-Sternberg, Anoop Ramgolam, Lliana Slevin, Lara Oversby and Debbie Cooper

Background: Despite the development of anaesthesia management guidelines, perioperative respiratory adverse events (PRAE) remain a major cause of morbidity and mortality during paediatric anaesthesia causing more than three quarters of critical incidents and nearly one third of all perioperative cardiac arrests. Perioperative respiratory adverse events include laryngospasm, bronchospasm, stridor, severe coughing, oxygen desaturation and airway obstruction. Improving the identification of children at risk of PRAE during the pre-anaesthetic assessment and developing perioperative preventive strategies incorporated into an optimised anaesthetic management would reduce the occurrence of PRAE.

Early results have demonstrated that exhaled nitric oxide can predict adverse events during anaesthetia, but that it is no better than asking children and their parents a detailed medical history. Other current work is looking at the best way to administer anaesthetic agents and if using salbutamol (for example Ventolin) before surgey reduces adverse events.

This project is funded by the National Health and Medical Research Council of Australia, State Health Research Advisory Council and Princess Margaret Hospital Foundation

Clinical

COLLATION OF MULTI CENTRE PLETHYSMOGRAPHIC LUNG VOLUMES DATA TO DERIVE REFERENCE EQUATIONS FOR CAUCASIAN CHILDREN.

Maureen Verheggen, Graham Hall

Knowing what a normal result is for any medical test is essential. Equally this applies for the interpretation of any lung function test. We are working towards a global multicentre normal range for lung volumes in children. The aim of this study is to derive reference ranges for static lung volumes based on age height and sex, for contemporary health Caucasian children as a multi centre project with collaborators in Europe and New Zealand. We have collated data from five centres (Perth, Australia; Christchurch, New Zealand; London, England; Berne, Switzerland and Utrecht, The Netherlands) and equations were successfully derived for a rage of static lung volume outcomes.

ASSESSING THE ACCURACY OF THE HYPOXIA CHALLENGE TEST TO PREDICT IN-FLIGHT HYPOXIA IN INFANTS

Graham Hall, Maureen Verheggen

Each year many infants born prematurely undertake air travel to return home after treatment at KEMH or PMH or for holiday travel. Air travel exposes babies to reduced oxygen levels on the aircraft. Whilst for most of us this is well tolerated, the effect of this reduced oxygen level on babies born prematurely has not been scientifically evaluated. The hypoxia challenge test, which is used to assess fitness to fly in patients with respiratory disease, has shown to replicate in-flight hypoxia in adults but in newborn infants has demonstrated to be inaccurate. It is not known if it is accurate in predicting the need for in flight oxygen in preterm infants up to 12 months corrected age. The aim of this study is to determine the accuracy of the Hypoxia challenge test in predicting in-flight hypoxia in pre-term and healthy term infants.

Staff and Students

HEAD OF DIVISION

Graham L. Hall; BAppSci, PhD, CRFS, FANZSRS

Research Strategy Leader, Telethon Kids Institute

Professor (Adjunct), Centre for Child Health Research, University of Western Australia

Associate Professor (Adjunct), Faculty of Health Sciences, Curtin University

Research Staff

Ms Georgia L Banton BSc - Research Assistant

Mrs Debbie Cooper - Research Assistant

Ms Naomi Hemy - Research Assistant

Mr Chris O'Dea B. Med Sci (Resp Hsci) Hons – Senior Respiratory Scientist

Ms Judy Park - BSc MBiostat

Dr Anoop Ramgolam - Research Officer

Dr Kathryn Ramsey BSc (Hons) PhD – Research Officer

Dr Shannon Simpson PhD – Research Officer

Ms Lliana Slevin BSc (Hons) - Clinical Trial Coordinator

Ms Maureen Verheggen - M Med Sci / Senior Respiratory Scientist

Dr Andrew Wilson - Paediatric Respiratory Physician

Postgraduate Students

Ms Afaf Al Bloushi BSc - PhD Candidate

Ms Karla M Logie BSc(Hons) - PhD Candidate

Mr Ash Mortavazi

Mr Chris O'Dea PhD, B. Med Sci (Resp Sci) Hons - PhD Candidate

Mr Tim Rosenow BSc Grad Cert Paed Resp Sci – PhD Candidate

Mr Mark Tan MSc - PhD Candidate

Ms Elisha White - MHltSci, CRFS.

RESEARCH SUPPORT

Ms Marina Stubbs – Administration Officer

THESES PASSED

Dr Karla M Logie BSc (Hons) "Structural and Functional Respiratory Abnormalities

in a Contemporary Cohort of 9 – 11 Year Old Children Born Very Preterm"

Awards

Chris O'Dea

Australian and New Zealand Society of Respiratory Scientist Advanced Education Grant 2013

Maddison Scholarship (Princess Margaret Hospital Foundation).

Kathryn Ramsey

Lung Institute of WA Glenn Brown Memorial Grant

Qantas New Investigator Award

ERS Grant for Best Abstract in Cystic Fibrosis Research

Shannon Simpson

Thoracic Society of Australia and New Zealand Janet Elder Award

TSANZ Travel Award; Awarded to attend the annual scientific meeting

Maureen Verheggen

ANZSRS WA Travel Award. To attend ERS Annual Scientific Congress 2013 in Barcelona to present work on improving lung volumes reference ranges.

External Committees

INTERNATIONAL

Graham Hall

- Joint American Thoracic Society - European Respiratory Society Working Party on Infant Lung Function Testing (2003-Ongoing)
- European Respiratory Society Global Lung Initiative Task Force: Co-Chair (2008 - 2012)
- Joint American Thoracic Society - European Respiratory Society Task Force for Provocation testing guidelines (2010 -Ongoing)
- European Respiratory Society Annual Congress Paediatric Respiratory Physiology Abstract review committee
- Associate Editor; Respirology (Oct 2012 – Ongoing)
- Editorial Advisory Panel; Expert Review of Respiratory Medicine (Oct 2006 – Ongoing)
- Secretary; Paediatric Respiratory Physiology Group, European Respiratory Society (Sep 2012 – Ongoing)

Kathryn Ramsey

- Joint American Thoracic Society – European Respiratory Society Working Group for the Standardisation of Inert Gas Washout Technique (2013 - ongoing)

NATIONAL

Graham Hall

Thoracic Society of Australia and New Zealand Professional Standards Sub-committee (2008 - 2013)

Member Medical and scientific advisory committee, Asthma Australia (2013 –)

Andrew Wilson

Member Medical and scientific advisory committee, Asthma Australia (2011 – 2013)

Co-ordinator of Paediatric Training, Specialist Training Committee for Thoracic and Sleep Medicine, Royal Australasian College of Physicians (RACP) (2008 –)

LOCAL

Graham Hall

Asthma Foundation of Western Australia Board member (2010 –)

Chair, Medical and scientific advisory committee, Asthma Foundation of Western Australia

Kathryn Ramsey

Postdoctoral Council, Telethon Kids Institute

Human Biology Advisory Board, Curtin University of Technology

Shannon Simpson

Postdoctoral Council, Telethon Kids Institute

2013-2014 Telethon Kids Leadership course member

Chris O'Dea

Thoracic Society of Australia and New Zealand WA state executive (2013).

Invited Presentations

Graham Hall

ERS Symposium: Conference Chair

South African Thoracic Society: Plenary: Global challenge of spirometry references ranges"

South African Thoracic Society: Symposium: "Clinical Utility of Preschool lung function

testing”

NACF

Shannon Simpson

Thoracic Society of Australia and New Zealand, WA scientific meeting

Rising Stars of Respiratory Science session “Pulmonary infection in infants with cystic fibrosis leads to progressive ventilation inhomogeneity”

Tim Rosenow

Tim Rosenow, “Quantitation of Chest CT Abnormalities in Early Life CF: Back to the Basics,” North American CF conference, Salt Lake City, October 2013.

Tim Rosenow “PRAGMA: a new method of quantifying structural lung disease in young children with cystic fibrosis,” TSANZ Branch Meeting, Perth, November 2013.

ACTIVE collaborations

Royal Perth Hospital, Respiratory Medicine, Perth

Dr Kevin Gain

King Edward Memorial Hospital, Neonatology, Perth

Prof Jane Pillow

Assoc Prof Noel French

Dr Ronnie Hagan

Dr Mary Sharp

University of Western Australia, Perth

A/Prof Dr Peter Franklin

A/Prof Sunalene Devadason

Royal Children’s Hospital, Melbourne

A/Prof Sarath Ranganathan

University Children Hospital, Zurich Switzerland

Dr Alex Moeller

University Children Hospital, Vienna Austria

Dr Fritz Horak

Institute for Child Health, London UK.

University College London

Prof Janet Stocks

University of Szeged, Hungary

Prof Zoltan Hantos

Erasmus University, Rotterdam, The Netherlands

Prof Philip Quanjer

Hospital for Sick Children, Toronto

Dr Sanja Stanojevic

University Medical Centre, Utrecht

Prof A Arets

Christchurch Hospital, Christchurch

Dr Maureen Swanney

Centre for Lung diseases, Berne

Prof Richard Kraemer

CYSTIC FIBROSIS

Overview

Imagine a world where you often have to miss school, playing sport and fun times with friends because your lungs don't work properly. You have to spend hours each day having treatments and getting a cold could potentially mean having to be admitted to hospital. This is what life can be like if you are child with cystic fibrosis (CF). CF is the most common chronic, life-shortening genetic condition affecting Australians. Approximately 1 in 25 people carry a CF-causing gene, resulting in around 1 in 2000 babies being born with the disease. CF affects many body systems, but is most devastating in the lungs, reducing a child's quality of life, and eventually leading to premature death.

AREST CF is a collaborative group of over 30 doctors, allied health professionals and researchers dedicated to improving the respiratory health of children with CF by translating scientific research into tangible clinical outcomes. The WA arm of the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) is based at the Telethon Institute and is led by Professor Stephen Stick.

Research by our group and others has shown that infants and children with CF exhibit reduced lung function and evidence of inflammation and infection at a very early age. This highlights the need for new treatments that can be given from time of diagnosis to prevent and/or reverse the damage.

EARLY SURVEILLANCE PROGRAM (ESP)

The ESP is the platform upon which the AREST CF research program is based. Children attending CF clinics in Perth and Melbourne participate in the ESP from the time of diagnosis onwards. The ESP includes bronchoalveolar lavage (BAL, to assess airway inflammation, infection and other markers of disease), imaging (CT scan, to measure structural lung disease) and lung function measurements. Researchers are able to track the progress of lung disease through a comprehensive longitudinal set of biological samples, images and data archives. The ESP is now embedded in standard clinical practice in both Australian centres, and is in the process of being adopted by centres in the Netherlands and Switzerland. In 2012, Professor Stick and A/Prof Sarath Ranganathan (VIC) were awarded a grant by US Cystic Fibrosis Foundation Therapeutics to maintain and expand this precious resource.

Funded by: NHMRC, US Cystic Fibrosis Foundation Therapeutics

EARLY DISEASE MECHANISMS

A better understanding of the significant contributing factors to the establishment and progression of CF lung disease will enable researchers to identify key targets for new treatments. Our research into early disease mechanisms combines data and samples from the ESP with cutting edge technologies for measuring airway biology and infection. New research projects in 2012 include investigations into mucus, hypoxia and the respiratory microbiome in progressive CF lung disease with the University of North Carolina, USA (NIH grant awarded in 2012) and the role of bioactive lipids in resolution of inflammation and tissue remodeling with Erasmus Medical Centre, Netherlands.

Funded by: NHMRC, NIH

PREDICTORS AND ENDPOINTS

The premise that underpins this research area is the identification of early predictors of adverse pulmonary outcomes in children with CF. This will allow treatments to be targeted at those who will benefit the most. Development of objective novel, safe and potentially more informative methods will allow clinicians to identify progressive lung disease earlier and prevent or delay the onset of abnormal lung structure and function. These methods can then be incorporated as outcome measures in clinical trials of new therapeutics. A/Prof Graham Hall's paediatric Respiratory Physiology team is a key element of this research, and partnering with A/Prof Sarath Ranganathan (Vic) and Professor Harm Tiddens (Erasmus MC, Netherlands) the team has been successful in obtaining funding from various sources in 2012 to investigate different aspects of lung structure/function and disease progression.

Funded by: NHMRC, NIH, UWA, Lung Institute of WA

DEVELOPING AND TRIALING NEW TREATMENTS AND INTERVENTIONS

A new research area for the group is the development of a stem cell program aimed at producing respiratory epithelial cells. These cells could be used to test candidate therapeutic compounds as well as a therapy to replace defective epithelial cells in CF patients. This program is being led by Dr Anthony Kicic, in partnership with researchers from UWA, Monash University and WEHI.

In March 2012, Professor Stick led a workshop sponsored by key international stakeholders. The workshop is the first stage of a collaborative process to reach consensus on clinical trial outcomes for young children with CF and to develop a research framework that addresses gaps in knowledge. Professor Stick proposed that COMBAT CF clinical trial, the first interventional trial for prevention of lung disease in infants, be adopted by this group as a template for trials of new therapeutics. Our goal is to eventually ensure that a clinical trial is available to every child born with CF.

Funded by: NHMRC, US Cystic Fibrosis Therapeutics

PSYCHOSOCIAL EFFECTS OF EARLY INTERVENTIONS

Little is known about the psychological, social and economic effects on families of children undergoing early interventions for CF. Examination of the risks, burdens and benefits for families will inform improved future strategies for appropriate clinical and pastoral care. Translation of this research will also impact on content and delivery of education, nature of support services offered and development of relationships between families and providers, improving service delivery and potentially health outcomes for children with CF. Collection of

qualitative and quantitative data from parents and care-givers of children participating in the ESP commenced in 2012 under the leadership of Dr Tonia Douglas, CF Centre Director at Princess Margaret Hospital.

Funded by: NHMRC, WA Department of Health

Staff and Students

HEAD OF GROUP

Professor Stephen Stick

Research Strategy Leader, Telethon Kids Institute

Senior Principal Investigator, Telethon Kids Institute

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

Head, Department of Respiratory Medicine, Princess Margaret Hospital

NHMRC Practitioner Fellow

CHIEF INVESTIGATORS

Professor Nicholas de Klerk (Biostatistics)

A/Professor Graham Hall (Paediatric Respiratory Physiology)

Dr André Schultz, (CF Centre Director, Princess Margaret Hospital)

Dr Tonia Douglas

RESEARCH STAFF

A/Prof Anthony Kicic – Research Officer, Associate Principal Investigator

Dr Ingrid Laing – Research Officer, Associate Principal Investigator

Dr Barry Clements – Paediatric Respiratory Physician, Department of Respiratory Medicine

Mr Marc Padro-Gossens ~ Data Manager

Ms Judy Park – Biostatistician

Ms Kathryn Ramsey - Research Officer, Paediatric Respiratory Medicine

Dr Shannon Simpson - Research Officer, Paediatric Respiratory Medicine

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Mr Luke Berry – Research Assistant

Ms Elizabeth Starcevich – Research Officer/study coordinator

Ms Georgia Banton – Research Assistant, Paediatric Respiratory Medicine

Ms Samantha Grogan – Research Assistant

Ms Anneli Robbshaw – Clinical Trials Coordinator

Ms Lucy McCahon – Clinical Trials Coordinator

Ms Caroline Gallagher - Research Officer, Paediatric Respiratory Medicine

Dr Clair Lee – Clinical Research Manager, Associate Program Manager

Ms Annemarie Naylor – Project Officer

Mr Thomas Iosifidis- Research Assistant

Mr Kevin Looi- Research Assistant

Ms Nicole Shaw-Research Assistant

Ms Alysia Buckley-Research Assistant

Ms Kelly Martinovich- Research Assistant

STUDENTS

Ms Clara Foo – PhD candidate

Mr Tim Rosenow – PhD candidate, Paediatric Respiratory Medicine

Ms Milena Jokic – PhD candidate

Mr Luke Garratt – PhD candidate

Ms Cindy Branch-Smith – PhD candidate

Mr Samuel Montgomery-Honours candidate

THESES PASSED

Dr Lauren Mott

Awards

Clair Lee

Mike Schon-Hegrad Award

Kathryn Ramsey

Lung Institute of WA Glenn Brown Memorial Grant

Qantas New Investigator Award

ERS Grant for Best Abstract in Cystic Fibrosis Research

Shannon Simpson

Thoracic Society of Australia and New Zealand Janet Elder Award

TSANZ Travel Award; Awarded to attend the annual scientific meeting

Cindy Branch-Smith

Friends of the Institute International Travel Award

Tim Rosenow

TSANZ (Branch meeting) Young Investigator

ERS Short term fellowship

Friends of the Institute International Travel Award

Annemarie Naylor

Friends of the Institute National Travel Award

AHRDMA travel award – Annual Scientific Meeting

AHRDMA best podium presentation – Annual Scientific Meeting

Invited Presentations

Stephen Stick

Thoracic Society of Australia and New Zealand 2013

NACF

Sophia 150 year symposium

Graham Hall

ERS Symposium: Conference Chair

South African Thoracic Society: Plenary: Global challenge of spirometry references ranges"

South African Thoracic Society: Symposium: "Clinical Utility of Preschool lung function testing"

NACF

Shannon Simpson

Thoracic Society of Australia and New Zealand, WA scientific meeting

Rising Stars of Respiratory Science session "Pulmonary infection in infants with cystic fibrosis leads to progressive ventilation inhomogeneity"

Tim Rosenow

Tim Rosenow, "Quantitation of Chest CT Abnormalities in Early Life CF: Back to the Basics," North American CF conference, Salt Lake City, October 2013.

Tim Rosenow "PRAGMA: a new method of quantifying structural lung disease in young children with cystic fibrosis," TSANZ Branch Meeting, Perth, November 2013.

Annemarie Naylor

Australian Health & Research Data Managers Association, Annual Scientific Meeting Adelaide March 2013

ACTIVE Collaborations

NATIONAL

A/Prof Sarath Ranganathan – Murdoch Children's Research Institute

Dr Phil Robinson – Royal Children's Hospital, Melbourne

Professor Peter Sly – Queensland Children's Medical Research Institute

Professor Ed Stanley – Monash University

Dr Ian Street – Walter and Eliza Hall Institute

Professor Linda Shields – James Cook University

Dr Lynn Priddis – Curtin University

Dr Yuben Moodley - UWA

INTERNATIONAL

Professor Ric Boucher, Dr Charles Esther, Dr Marianne Muhlebach, Professor Mike Knowles – University of North Carolina

Professor Bob Hancock – University of British Columbia

Professor Harm Tiddens – Erasmus University Medical Centre, Rotterdam

POPULATION SCIENCES

Overview

2013 was a busy year for researchers within the Division of Population Sciences.

In February, our researchers were identified as having a key role in a ground breaking, multi-million dollar Autism research centre. The Cooperative Research Centre for Living with Autism Spectrum Disorders will bring together the most respected Autism researchers and scientists from across Australia, including a Telethon Institute team. This new national research centre has been described as a game-changer in the ongoing fight to better understand the causes of autism and offer new hope to the families impacted by it. It is a massive step forward in developing national approaches to discovery, treatments and the development of support programs aimed at offering earlier and more accurate diagnosis of children with Autism Spectrum Disorder. This program of work began in July.

In March, Divisional researchers called for further investigation into a potential link between maternal smoking and childhood brain tumours. This followed the results of a new study which showed a possible connection between maternal smoking and increased risk of brain tumours in very young children. This research used data collected from the Australia Study of Childhood Brain Tumours to investigate whether parental smoking could be linked to the development of the disease in children. While the study backed up previous research showing little evidence between the two overall, it did indicate that maternal smoking before or during pregnancy could lead to an increased risk of childhood brain tumours in children less than 2 years of age. Our researchers did warn against drawing firm conclusions because the research was based on a small sample group of just over 300 families and further.

Also in March, our researchers showed that children with an intellectual disability or autism are up to ten times more likely to be admitted to hospital than unaffected children. The research team looked at more than one million hospital admission records from 416,611 Western Australian children born between 1983 and 1999. The study found an increased risk of hospitalisation varied from two to ten times that of the rest of the population. The burden was greatest for children with intellectual disability, particularly those with severe intellectual disability (children with an IQ less than 40 where the cause is unknown) where hospital admissions are ten times that of the general population. Hospital admission rates were not as high for children with autism but still higher than that of the general population. Children with autism are twice as likely to require hospitalisation, and for those who also had an intellectual disability, the rate was almost three times higher. Many of these children also have other medical conditions such as obesity, epilepsy, sleep or gastrointestinal problems or skin conditions. Our researchers call for more research into how these other underlying medical conditions relate to hospital admissions and ways to reduce the need for a hospital visit through primary care.

April was a busy month. Our researchers in a study aimed at assessing awareness and knowledge of justice professionals of Fetal Alcohol Spectrum Disorders (FASD) identified that up to 85 per cent of justice staff say responding to the needs of people with FASD is an issue in their work. FASD results from fetal exposure to alcohol. It is an umbrella term used to describe a range of cognitive, physical, mental behavioural, learning and developmental disorders. More than 75 per cent of judicial officers, 85 per cent of lawyers and Department of Corrective Services staff and almost 50 per cent of police officers who completed the survey perceived FASD as relevant to their work. Knowledge about FASD was highest among Department of Corrective Services staff who were more likely (44 per cent) to report having a good understanding of how FASD affects children and adults than participants from the other sectors. The study found widespread agreement (judicial officers 79 per cent and lawyers 92 per cent) that the assessment and diagnosis of FASD would improve the possibilities for young people with FASD and would prevent their continued enagement with the justice system over time. Divisional researchers recommend greater awareness, better training and education and alternate sentencing options that consider the neurocognitive impairments associated with FASD.

Also in April, our researchers published the results of a study that revealed a potential link between professional pesticide treatments in the home and a higher risk of children developing brain tumours. The study found that exposure by parents to professional pesticide treatments prior to conception could increase the chances of a child developing a brain tumour. The study involved the analysis of data from 303 case families and 941 control families who participated in the Australian Study of Childhood Brain Tumours (Aus-CBT) -- a nationwide case-control study designed to investigate environmental and genetic risk factors for CBT. The study examined professional pesticide exposure in the year before pregnancy, during pregnancy and after the child is born, revealing a link between the timing of the exposure and the type of pesticides involved. The results indicated that parents' exposure to professional pest control treatments in the home up to a year prior to falling pregnant is associated with an increased risk of their child developing a brain tumour. Our researchers recommended that parents avoid exposure to professional pest control treatments in the period leading up to conception. However, the results do not necessarily mean that pesticide exposure had caused brain tumours in children in the study as there are likely many causes of childhood brain tumours.

Still in April, our researchers published a study looking at testosterone levels and child behaviour that found that testosterone levels in the womb have little impact on later childhood behavior. The impetus for this research was findings from smaller studies that suggested high levels of testosterone may predispose children to more masculine behaviour, where low levels might predict more feminine behaviours. Our study was comparetively large compared to previous studies and did not find any significant differences in behaviour as a result of differing exposure to testosterone in the womb. The study comprised 430 females and 429 males from the Western Australian Pregnancy Cohort (Raine) Study where umbilical cord blood had been collected. Total testosterone concentrations were determined by mass spectrometry and bioavailable testosterone

(BioT) levels were calculated. Our researchers analysed bioavailable testosterone (BioT) in maternal cord blood collected at delivery and assessments of the child's behaviour at age 2, 5, 8 and 10 years. We found no effect of high or low bioavailable testosterone levels in cord blood on later child behaviour.

Finally, our researchers showed that a Western diet is associated with an increased risk of liver disease in teenagers. The research findings were published in April's edition of prestigious international journal The American Journal of Gastroenterology. The study looked at dietary patterns and liver ultrasounds of almost 1000 teenagers from the long-term Raine Study. Our researchers found that a Western style of diet was associated with an increased risk of non-alcoholic fatty liver disease (NAFLD) at 17 years of age and a healthy diet was protective, particularly in obese adolescents. NAFLD is a very common condition that can progress to cirrhosis, liver cancer and liver failure in a small proportion of individuals. In rare cases, people may require liver transplantation. The study results show that 15 per cent of adolescents had NAFLD. More than half of those with NAFLD were overweight or obese. A "Western" diet is characterised by a high intake of takeaway foods, red meat, confectionary, soft drinks, processed, fried and refined foods; while a "healthy" pattern is a diet high in fresh fruit and vegetables, whole grains, legumes and fish. Our researchers concluded that efforts to reduce obesity in childhood and adolescence may be important for preventing NAFLD.

In May, Divisional researchers found that the prevalence of mental health disorders in parents of infants rose dramatically between 1990 and 2005. Ourresearchers studied de-identified linked health data for all parents of infants born in WA between 1990 and 2005. They looked at data on hospitalisations and outpatient clinic visits for mental health problems at any time before the birth of a child and in the year before a child's birth year. They found that overall, prevalence of prior mental health disorders in mothers increased, from 76 per 1000 births in 1990 to 131 per 1000 births in 2005. There was an estimated 3.7% increase per year in the odds of children being born to mothers with a prior mental health disorder. In addition, there was an increase in prevalence of prior mental health disorders in fathers, from 56 per 1000 births in 1990 to 88 per 1000 births in 2005 (3.1% increase in odds per year). It has long been established that parental mental health can impact children's outcomes which not only relate to children's own mental health but also language development, behaviour and physical health. Our study is the first in Australia to investigate the population prevalence of previous and current mental health disorders in parents, including trends over time. In explaining these results, our researchers suggest that broader service availability in WA, and better data collection could be reasons for the increases. However, some of the increase could be a true increase in the prevalence of mental health disorders in parents. The results of our study indicate that it is important for parents to seek treatment and support for their mental health issues to alleviate the symptoms they experience and reduce the impact their symptoms may have on their children and family.

Also in May, our researchers found that the gap between life expectancy in patients with a mental illness and the general population has widened since 1985 and efforts to reduce this gap should focus on improving physical health. The higher death rate associated with mental illness has been extensively documented, but most of the attention has focused on the elevated risk of suicide, whereas our study found that most of the risk can be attributed to physical illness such as cardiovascular and respiratory diseases and cancer (80% of deaths). Data were taken from population-wide databases covering Western Australia as well as Mental Health Information Systems and Death Registrations. Our researchers compared life expectancy in the cohort of psychiatric patients with life expectancy at birth for the total Western Australia population (published by the Australian Bureau of Statistics). Although suicides represented a large proportion of excess deaths for patients with mental illness, physical conditions represent the majority of excess deaths. Cardiovascular disease was the main cause particularly for patients with schizophrenia (32% males, 46% females), other psychoses (33% males, 41% females) and neurotic disorders (38% males, 38% females).

Our researchers suggest that while strategies aimed at the prevention of suicides remain an important component, 80% of excess deaths are associated with physical conditions and that multi-pronged approaches will be required to address these inequalities. We also stressed that treating both physical health problems and risk factors would result in improvements to both physical and mental health.

The month of May also saw the announcement that the second national survey to look at the mental health and wellbeing of Australian children and adolescents was underway, with data collectors out and about across the country. This survey, "Young Minds Matter" is funded by the Australian Government through the Department of Health and Ageing and is being conducted by researchers within the Division. The results of the survey will be used to help plan, shape and develop programs and support services for Australia's children and adolescents, building on the successful work of the first survey carried out in the late 90's. This second survey will be instrumental in shining new light on how the kids of today are coping with new challenges and new pressures in a changing world.

In June our researchers found that the impact of long-term unemployment and separation in a family extends to future generations. Divisional researchers looked at two particularly disruptive family history events, joblessness and separation, and the impact of these on the social and emotional wellbeing and academic achievement of study children. The research showed the effects of joblessness and separation experienced by grandparents extended beyond the outcomes of their own children (the study parents) into the next generation as well (the study children, or grandchildren). Irrespective of whether or not the study parents had experienced joblessness, the outcomes for children whose grandparents had experienced joblessness were significantly worse than those whose grandparents had not experienced joblessness. A similar pattern was shown for family separation, but only in families where the study parents had separated. That is, family separation in the grandparent generation was

only associated with poorer outcomes for study children if the study parents had also separated. Our researchers suggest that the results demonstrate how challenging family circumstances can persist across generations.

Also in June, researchers from the Division released the results of study showing teenagers who drink more than one standard can (375g) of sugary drinks a day are putting themselves at higher risk of developing type 2 diabetes and cardiovascular disease, such as heart disease or stroke, later in their lives. The study found that teenagers who drank about a can of soft drink a day had lower levels of 'good' cholesterol and higher levels of the 'bad' triglyceride form of fat in their blood, regardless of whether they were overweight. The study, published in the latest edition of The American Journal of Clinical Nutrition, followed more than 1,400 teenagers aged between 14 and 17 years from the Western Australian Pregnancy Cohort (Raine) Study. The study shows that greater intakes of sugary drinks may put young people on a path to the early development of risk factors associated with diabetes and cardiovascular disease.

On a related topic, a new study by our researchers ignited calls for better collection of data on food sugar levels as part of the ongoing battle against rising obesity. The results of a study by Divisional researchers published in July found a very large increase in the volume and value of imported sweetened products into Australia over that time. The study took into account all forms of sugar in the diet - refined sugar as well as sugar added to manufactured or processed food or drinks imported into Australia. Our research suggests that per capita sugar consumption has been increasing since 1988 and this may well be having an impact on the dietary health of our nation. Our research refutes the 'Australian Paradox' which was suggested by an earlier study that reported a drop in Australian sugar consumption alongside a rise in obesity rates.

In July, it was announced that our researchers were members of a consortium that was awarded an Australian Research Council (ARC) Linkage Grant to develop a new measure of how well Australian children are doing during middle childhood. The Middle Years Development Instrument (MDI) is a validated population-level measure of well-being in middle childhood. It was designed in Canada at the University of British Columbia, to provide schools and communities with pragmatic data to inform policies and practice. Our study aims to adapt and psychometrically validate the MDI for use in Australia, including culturally adapting the tool for Australian Aboriginal children. The tool has great potential to provide educators, parents, researchers, and policy makers with much needed information about the psychological and social worlds of children.

In September, research conducted in the Division found new clues into language development by identifying risk factors for receptive language development in Australian children. The study looked at the receptive language of 4332 children between four and eight years of age from the Longitudinal Study of Australian Children (LSAC). Receptive language or vocabulary is the ability to derive meaning from words and builds the foundation for language acquisition and literacy. Low receptive language ability is a risk factor for under-achievement at school. Our research team looked at a wide range of child, maternal and family influences on receptive language development from four to eight years of age and found a range of factors were associated with receptive language delay at four years of age including the mother being from a Non- English Speaking Background (NESB), low school readiness, child not read to at home and the child having four or more siblings. However, none of these risks were associated with a lower rate of growth in the child's language from four to eight years. Our researchers were surprised to see that the children with lower language abilities at four years of age, had more rapid language development growth than other children; however, they never completely catch-up to their peers. The research also showed that socio-economic disadvantage was not a risk factor for low receptive vocabulary ability at four years but was the only risk factor associated with a lower rate of growth in receptive vocabulary ability. Our researchers have recommended a whole-of-community approach to tackle language problems in children. Community-wide programs are needed to address language problems as it's very difficult to predict which kids will or won't have delay in their language. This is a responsibility for everyone - parents, schools, communities and government.

Also in September, a new study by our researchers found a link between energy drink consumption in young men and increased anxiety. The study examined the association between energy drink consumption and mental health in young adults from the Western Australian Pregnancy Cohort (Raine) Study. The research showed that energy drink consumption was significantly associated with anxiety in males and that this research supported previous studies that identified energy drinks as being a potential risk factor for mental health problems in young men. Our research showed that drinking one 250ml can or more a day of energy drinks is associated with increased anxiety and the association gets stronger as energy drink consumption increased. The study showed no such association in the female group and researchers believe this may be related to a higher rate of energy drink use amongst young men than young women.

In November, our researchers found that symptoms of depression in young men may be associated with low vitamin D levels. The study examined the association between vitamin D levels and mental health in young adults from the Western Australian Pregnancy Cohort (Raine) Study. Our research showed that low vitamin D levels were associated with increased symptoms of depression in males and that this research supported previous studies that identified the link between vitamin D levels and brain activity. We are unsure as to why the link exists between depression and vitamin D levels in young men but not young women and that further research is needed to examine the relationships further.

In December, the world's largest study of gastroenteritis trends in children, conducted by researchers within the Division has shown the disparity between Aboriginal and non-Aboriginal health may be improving. The study examined gastroenteritis hospitalisation trends in almost 600,000 West Australian Aboriginal and non-Aboriginal children over two decades. Gastroenteritis or infectious diarrhoea is a leading cause of illness and death globally,

causing more than 800,000 deaths in children under five, mainly in the developing world. The study results show that, between the periods 1983-1994 and 1995-2006, the hospitalisation rate for gastroenteritis dropped significantly in young Aboriginal children with a 42% decline in those aged 12-17 months and a 36% decline in those aged 18-23 months. In contrast, over the same time periods, the rates of gastroenteritis hospitalisation increased significantly in non-Aboriginal children with a 34% increase in those aged 18-23 months and 25% increase in those aged 2-4 years. While the rate of gastroenteritis in Aboriginal children has declined substantially, the gap between Aboriginal and non-Aboriginal children continues. There were several possible reasons for the observed decline in hospitalisations for gastroenteritis including general improvements in Aboriginal health and hygiene including water quality and sanitation, and reduced overcrowding. The study results also showed gastroenteritis hospitalisations rates varied between different climatic zones and geographical regions. For Aboriginal children under five living in the tropical Kimberley and Pilbara-Gascoyne regions, rates were around 3.5 times higher than in metropolitan Perth. For non-Aboriginal children under 5, rates were 30-60% higher in rural and remote regions than in Perth. This highlights the continuing need to address poor health outcomes in all children living in remote areas and provide them with better access to medical and health services.

Also in December, research conducted by our researchers found maternal smoking during pregnancy to be an important risk factor in Attention Deficit Hyperactivity Disorder (ADHD). The study of 12,991 West Australian children diagnosed with ADHD found that, compared with mothers whose children did not have ADHD, mothers of children with ADHD were significantly more likely to be younger, single, smoked in pregnancy, had some complications of pregnancy and labour and were more likely to have given birth slightly earlier. It did not make any difference if the child was a girl or a boy. ADHD is the most common neurodevelopment disorder affecting 5.2% of children worldwide with well-known clinical consequences and functional outcomes that can affect individuals throughout their lifespan. The study found a strong genetic predisposition to ADHD, as well as some evidence of early environmental and maternal factors playing a part. Our research is one of the largest population-based studies to date, and uses a careful clinical definition of ADHD and links a range of data sets, which overcome many of the limitations of previous studies. We found that certain maternal factors did increase the risk of ADHD in the child with smoking during pregnancy being a significant risk factor. Other factors such as low birth weight, giving birth at greater than full term, and low Apgar scores in the baby were not associated with an increased risk of ADHD in the child. Our study identified broad risk factors rather than causes and that the information could not be used to identify the factors associated with any particular child's disorder.

Finally, in December, ending the year on a high, it was announced that researchers from the Division will play a significant role in a new multi-million dollar Centre for Excellence aimed at investigating - and breaking - the generational cycle of social disadvantage. Our researchers will take a lead role in the new centre in recognition of our continued role and influence in working to improve the lives of children and outstanding statistical and data management experience. This Centre for Excellence will be a huge step forward in tackling serious poverty and disadvantage in this country and will work at breaking the cycle of welfare dependency. It will look at how better education opportunities will help the next generation break free from disadvantage and also investigate and identify early childhood intervention programs. This ARC Centre of Excellence for Children and Families over the Life Course will come into operation during 2014.

Birth Defects and Developmental Disorders

PHARMACOVIGILANCE IN PREGNANCY USING POPULATION-BASED LINKED DATASETS

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

New medicines are not usually trialled on pregnant women before release so it is important to have ways to monitor their safety. This project uses data linkage of population-based health datasets from Western Australia and the national pharmaceutical claims dataset, the Pharmaceutical Benefits Scheme, to investigate pregnancy outcomes for women and their children (N=96,698 pregnancies). Medicines are analysed by drug category and at the individual medicine level.

The safe use of antidepressants in pregnancy is an ongoing issue for clinicians with previous studies reporting that around 10% of pregnant women suffer from depression. As the birth admission will be the first admission to hospital during their pregnancy for most women, their use of antidepressants, or their depressive condition, may not be revealed to the attending hospital clinicians. This may result in adverse outcomes for the mother and infant. From our data, 80% of women dispensed an antidepressant did not have depression recorded as a comorbidity on their hospital records. A simple capture-recapture calculation suggests the prevalence of depression in this population of pregnant women to be around 16%. This study concluded that no single data source is likely to provide a complete health profile for an individual. For women with depression in pregnancy and dispensed antidepressants, the hospital admission data do not adequately capture all cases.

We also considered the off-label use of ondansetron in pregnancy. Nausea and vomiting of pregnancy is the most common medical condition in pregnancy. There is an increasing trend to prescribe ondansetron although its safety for use in pregnancy has not been established. The women dispensed ondansetron were more likely to be privately insured (OR: 5.8; 95% CI: 4.3–7.9), to be Caucasian (3.3; 1.9–5.7), not to smoke during their pregnancy (2.9; 1.8–4.7), to have a multiple birth (2.7; 1.5–5.0), and to have used fertility treatment (1.8; 1.0–3.4). There was a small but not significantly increased risk of a major birth defect with first trimester exposure (1.2; 0.6–2.2). Our study did not detect any adverse outcomes from the use of ondansetron in pregnancy but could not conclude that ondansetron is safe to use in

pregnancy.

Linked administrative data is an important means of pharmacovigilance in pregnancy in Australia. Data linkage provides a rich resource at a relatively low cost and in a more timely manner, than other pregnancy studies in pharmacovigilance whilst maintaining confidentiality.

Funders of the project: NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).

FOLATE AND PREVENTION AND NEURAL TUBE DEFECTS

Carol Bower, Heather D'Antoine, Susannah Maxwell, Kate Brameld, Siobhan Hickling, Julia Marley, Peter O'Leary.

In September 2009, Australia implemented mandatory folic acid fortification of wheat flour for bread-making to reduce the incidence of neural tube defects. Aboriginal infants have a higher risk of neural tube defects than non-Aboriginal infants in Australia.

Prior to mandatory fortification we undertook a study to estimate baseline folate status in Aboriginal and non-Aboriginal people attending health services in metropolitan and regional WA. In 2013, we repeated the study in order to assess the effect fortification has had on folate status. Data collection is complete for Aboriginal participants and close to completion for non-Aboriginal participants. Analysis will be undertaken in early 2014. Western Australian data on the incidence of neural tube defects are contributing to a national study, also due for completion in 2014.

Funders: Healthway Project Grant #17424; NHMRC Fellowship #634341, NHMRC Program Grant #572742; Department of Health WA.

DEVELOPING CLINICAL GUIDELINES FOR THE MANAGEMENT OF GASTRO-INTESTINAL DISORDERS AND BONE HEALTH IN PATIENTS WITH RETT SYNDROME

Jenny Downs, Helen Leonard, Gordon Baikie, Madhur Ravikumara, Nusrat Naseem, Deirdre Croft, Amanda Jefferson, Helen Woodhead, Sue Fyfe, Aris Siafarikas

Rett syndrome is frequently associated with poor growth, feeding difficulties and problems with gastro-oesophageal dysmotily such as reflux, constipation and abdominal bloating. There is limited literature on management strategies for these common gastro-intestinal conditions in Rett syndrome and we have previously used the Delphi technique to develop a consensus for items that describe their assessment and management. Our set of recommendations for the assessment and treatment of gastro-intestinal issues has been the subject of three publications on the topics of poor growth, dysmotility and gall bladder disease in Rett syndrome. We have also produced a lay booklet that presents the guidelines in a format suitable for families together with two leaflets for clinicians on the topics of poor growth and dysmotility. These have been disseminated to all families with a daughter with Rett syndrome in Australia, is available on our Telethon Kids Institute website, and has been additionally disseminated by family associations in the US and UK.

Rett syndrome is also associated with osteoporosis and a greater likelihood of fracture in comparison with the general population. We recruited a panel of 35 expert clinicians and researchers and again used the Delphi technique to develop guidelines for optimal bone health in Rett syndrome. A manuscript describing this research is in preparation and we envisage writing a lay booklet and clinician leaflet for dissemination of findings as we did for the gastrointestinal guidelines.

Funder of the project: Rett Syndrome Association UK.

TOWARDS EVIDENCE BASED CARE FOR RETT SYNDROME: A RESEARCH MODEL TO INFORM MANAGEMENT OF RARE DISORDERS

Helen Leonard, John Christodoulou, Carolyn Ellaway, Helen Woodhead, Jenny Downs, Elizabeth Geelhoed, Elizabeth Elliott, Peter Jacoby, Ian Torode, Gordon Baikie, Mark Davis, Bruce McPhee, Madhur Ravikumara, Sue Thompson, Margaret Thomson, Ami Bebbington, Amanda Jefferson, Sonya Girdler, Anna Urbanowicz, Kingsley Wong, Catherine Bunting, Caitlin Marr, Orla McIlroy, Geoff Askin, Maree Izatt

Rett syndrome is a rare neurological disorder usually affecting females and caused by a mutation in the MECP2 gene. AussieRett, as the Australian Rett Syndrome Study is known, is a population-based study which, since 1992, has followed 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.

We are currently in the final year of an NHMRC funded study commenced to facilitate best practice in clinical decision making, laboratory procedures and counseling in relation to the diagnosis and management of Rett syndrome. This study aims to:

- develop recommendations for the diagnosis process for Rett syndrome;
- identify longitudinal changes in gross motor abilities, hand function and development of scoliosis and;
- evaluate the clinical effectiveness of scoliosis and gastrostomy surgery in children and adults with Rett syndrome.

For the diagnostic study questionnaires relating to the characteristics of their patients have been completed by 134/141 clinicians who requested MECP2 testing from one of the three Australian accredited laboratories for 225 patients. These are completed prior to the result of genetic testing being known. The goal is to develop tools to support clinical decision making to facilitate timely diagnostic testing for girls with Rett syndrome, thereby assisting families in the often stressful early stage when seeking a diagnosis. Data collection has been continuing since July 2011 and will continue through 2014.

As part of the longitudinal study follow-up questionnaires were administered in September 2011 to 269 families enrolled in the study and

families could return data online, on paper or during a telephone interview. The response fraction from parents and care-workers has been excellent at over 86% and we are also receiving some additional family data. Information has been collected on the affected individual's functional ability in daily living, behaviour, hand function, medical conditions, use of health and education services, and family health and functioning. Questions have also been included to assess parental satisfaction with spinal fusion and gastrostomy procedures for those children and adults who have undergone these procedures.

Scoliosis is a common complication of Rett syndrome, however little is known about the natural history of curve progression and the relationship with the type of genetic mutation, age and mobility level. X-ray data on the progression of the spinal curve of children and adults with scoliosis has been collected on 195 girls and women with scoliosis and there will be some additional data collection throughout 2014. Spinal fusion (for scoliosis) and gastrostomy insertion (feeding tube into the stomach due to problems with swallowing or poor growth) are surgeries faced by many children and adults with Rett syndrome. The decision to proceed with these surgeries is often difficult for families, and both clinicians and families need accurate information about the short and long term risks and benefits of these procedures. Currently, there are gaps in our knowledge of outcomes. Collection of data from the hospital records is near completion and will supplement the questionnaire data. We are also collecting video data and by year end 2013 135 families had already provided video footage of their daughter's functional abilities. Video data collection will also continue through 2014.

The AussieRett study has continued to involve consumers through the Consumer Reference Group, biannual newsletters and online via the new website and Facebook page. The Consumer Reference Group, involving family members from across Australia via regular teleconferences, is an opportunity to discuss and give valued feedback on all facets of the study.

The study has a multi-disciplinary investigative team from the fields of medicine, physiotherapy, epidemiology, biostatistics, dietetics and occupational therapy. It has national collaborations with the Children's Hospital at Westmead and the Children's Hospital Randwick, Sydney, the Royal Children's Hospital, Melbourne, the Mater Children's Hospital, Brisbane and the Royal Children's Hospital, Brisbane. We will shortly have collaborations with clinicians at the Women's and Children's Hospital, Adelaide and the Monash Hospital, Melbourne.

During 2013 fourteen articles relating to Rett syndrome were published or accepted for publication by our group. These articles included investigations of epilepsy, poor growth, gastrointestinal dysmotility, gallbladder disease and the regression period in Rett syndrome. We have also investigated participation in activities in the community and have written a review on hand function in Rett syndrome. Another study recruited families with a daughter with Rett syndrome in China and examined caring during everyday life.

Funders of the project:

Current: NHMRC Project Grant (1004384), NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

INTERNATIONAL RETT SYNDROME STUDY: INTERRETT 2013

Helen Leonard, Alison Anderson, Ami Bebbington, Nada Murphy, Jenny Downs, Heidi Meyer, Nan Hu.

Rett syndrome is a rare neurological disorder which has an incidence of diagnosis of 1:9000 by the age of 32 years and is associated with mutations in the MECP2 gene. Given the low number of cases at a national level (~415 in Australia) international collaboration and data collection are imperative. The InterRett database project allows clinicians and families caring for an individual with Rett syndrome to directly contribute to the global research effort by completing web or paper-based questionnaires. The project, which is funded by the International Rett Syndrome Foundation, was established in 2002 and continues to grow and expand with online questionnaires available in Mandarin and six European languages. The database currently contains ~ 2,750 cases representing over 50 different countries. New participants register using a form on the project website (also available in different languages). International support for the InterRett project continues to strengthen, particularly in China and we have a Chinese national, Nan Hu who is providing translational expertise and assisting families in submitting their information. The website also allows users to: generate graphs based on summary data; download clinical guidelines for the management of scoliosis and gastrointestinal issues; and to read snapshots of the over 20 peer-reviewed publications arising from analyses of the InterRett data. Our research covers a wide range of topics such as: pain sensitivity; the characteristics that influence diagnosis; diagnostic challenges in China; the influence of mutation type or DNA variations in the BDNF gene on clinical severity; and ageing and survival in Rett syndrome. To allow families to contribute at all levels of the research process, from study design to the dissemination of findings, a Consumer Reference Group (CRG) has been established. In 2013, CRG representatives from the US, UK and Australia successfully provided their input during two teleconferences. This highly successful framework for the collection of data for a rare disorder on a global scale has been replicated for the rare CDKL5 disorder and is now being developed for MECP2 duplication syndrome.

THE NATURAL HISTORY OF THE CDKL5 DISORDER: DEVELOPMENT OF AN INTERNATIONAL REGISTER

Stephanie Fehr, Helen Leonard, John Christodoulou, David Forbes, Simon Williams and Jenny Downs

The CDKL5 disorder is caused by mutations on the cyclin-dependent kinase-like 5 (CDKL5) gene. Clinical features include early-onset seizures (generally within the first three months of life), global developmental delay, abnormal muscle tone, hand stereotypies, gastrointestinal problems and bruxism. In the past this disorder was considered an atypical form of Rett syndrome, however our research published in 2012 and other articles published since conclude

that it is an independent disorder.

Since our 2012 publication, which included the largest cohort of individuals with the CDKL5 disorder, we worked on developing an International database for the CDKL5 disorder. This was done in collaboration with the International Foundation for CDKL5 Research. Data collection commenced in September 2012 and involved families of individuals with the CDKL5 disorder completing a questionnaire either online or on paper. The questionnaire has also been translated into French, German and Spanish. By year end 194 families had been recruited and 77 had already completed the questionnaire with a further 50 in progress. In October 2013 we presented some initial preliminary findings at the 3rd European Rett syndrome Conference in Maastricht. We investigated the functional abilities of individuals with the CDKL5 disorder, the occurrence and impact of gastrointestinal problems and the treatment and pattern of epilepsy. These findings were also included in our first International CDKL5 disorder database newsletter sent to all participating families and clinicians. Data collection will continue in 2014 and we plan on presenting our findings at the 2nd International CDKL5 Research Symposium and Family Conference in Washington in June 2014.

Funders of the project: Nil

DOWN SYNDROME CLINICAL TRIAL- BTD-001

Helen Leonard, Jenny Downs, Jenny Bourke, Peter Richmond, Jasminka Murdzoska, Kingsley Wong, Tanya Stoney, Gabi Willis, Barbara Anderson

The purpose of the study is to determine if a new formulation of the drug called BTD-001, which behaves as a GABA antagonist, can improve function and cognition in people with Down syndrome. This randomized, double blind, placebo-controlled trial is assessing the safety and preliminary efficacy of the drug. The study involves taking an oral formulation of BTD-001 for 12 weeks and undergoing cognitive tests over 7 clinic visits. Participants are monitored for adverse events for the duration of the study.

The study is being conducted in eight sites across Australia. For our site study participants have generally been contacted through the Down Syndrome NOW database developed at the Institute through previous survey studies involving families with a child with Down syndrome. Participants must be aged 13-35 years, be able to complete the required cognitive tests and be screened for current medical conditions such as epilepsy and hypothyroidism, which may indicate exclusion from the study. Currently thirteen individuals have been screened and eight have been randomized.

IDEA - INTELLECTUAL DISABILITY EXPLORING ANSWERS

Helen Leonard, Jenny Bourke, Ami Bebbington, Patrick Fitzgerald, Amanda Langridge, Geoff Hammond, Deirdre Croft, Carol Bower

The IDEA Database provides an infrastructure for population-based epidemiological research into the causes and prevention of intellectual disability as well as the outcomes for those affected. Information in the database is sourced from data from the Disability Services Commission (DSC) since 1953, as well as information from the Department of Education for children born since 1983. IDEA has been updated with notifications of children identified with an intellectual disability from the Department of Education and the Disability Services Commission to the end of 2010. These records are linked by the Western Australian Data Linkage Unit (DLU) to each other and to all current notifications on the database in order to minimise any duplications. Medical information on cause of intellectual disability is provided from Disability Services Commission.

The current prevalence for intellectual disability calculated on the WA births from 1983-2003 and ascertained up to 2010 is estimated to be 17.4/1000 live births. This is an increase on the earlier prevalence estimate of 14.3/1000 live births, calculated using births from 1983-1992 and ascertained up to 1999. These data suggest that the prevalence of mild-moderate intellectual disability may have increased among children born in the nineties. This will be further investigated to try to identify the reason for this rise and whether it might relate to an increase in the diagnosis of autism spectrum disorders or another cause.

Recent articles published in the scientific literature using data from the IDEA database have investigated hospitalisations in children with intellectual disability and autism, and shown an increased risk of hospitalisation in childhood which varied from 2 to 10 times that of the rest of the population. A further study investigated the pattern of hospitalisations for children with Down syndrome and found respiratory and ear infections were the most common reasons for admission. These important findings can inform service planning and resource allocation for these children with special needs. A book chapter, which outlined the value of linked data for intellectual disability research, was published in the International Review of Research in Developmental Disabilities. A report on the IDEA Database over the last 10 years has also been drafted and will be published early in 2014.

Investigations currently underway include: the causes of hospitalisation for children with intellectual disability and autism; exploring the pathways to contact with Juvenile Justice for Aboriginal children in order to support a strategy for change; the relationship between a woman's psychiatric history and the likelihood of her subsequent offspring developing intellectual disability or autism; and the co-occurrence of intellectual disability, cerebral palsy and birth defects.

The IDEA Database is overseen by the IDEA Advisory Council. The 2013 membership included Professor Carol Bower (Chair), Dr Helen Leonard, Jenny Bourke, (TICHR), Dr Vera Morgan (UWA), Richard Sanders (Department of Education), Nick Cantatore (DSC), Dr Peter Rowe (State Child Development Centre) and Charlie Rook (Consumer, who sadly passed away December, 2013).

Funders of the project: Disability Services Commission.

DETERMINANTS AND OUTCOMES OF PRETERM BIRTH & PATHWAYS INTO DEVELOPMENTAL DISORDERS

Fiona Stanley, Helen Leonard, Geoff Hammond, Amanda Langridge, Kristjana Einarsdottir, Ami Bebbington, Jenny Bourke, Nick De Klerk, Peter Jacoby, Steve Ball, Gavin Pereira, Eve Blair

Increases in preterm birth and survival over time of those born pre-term are occurring due to a range of factors. These include increasing maternal age and co-morbidity (particularly obesity and maternal diabetes), increases in multiple births, social factors such as higher fertility rates in socially disadvantaged high risk mothers and changes in obstetric practice relating to reproductive technologies, early induction of labour and use of caesarean section. Our group undertakes complex statistical analyses principally using linked deidentified Western Australian population data relating to pregnancies, births and hospitalisations to investigate the determinants and outcomes of preterm birth and the pathways leading to developmental disorders. We have already shown how the determinants of both spontaneous and medically indicated pre-term births are changing over calendar time. We have also compared neonatal outcomes for babies born pre-term in the public and private systems. Interestingly following the Australian Private Health Insurance Incentive policy reforms, which were implemented in 1997–2000, births in privately insured patients and also caesarean deliveries increased. We also showed that from 1996 to 2005, the rising caesarean delivery rate in nulliparous women could mostly be attributed to an increase in prelabour caesarean deliveries for private patients delivering in private hospitals. Our current work also includes investigations of the relationship between various environmental and geographic factors and pregnancy complications and birth outcomes.

Further to our examination of the causes of pre-term birth, the next step will be to follow these vulnerable infants born at different gestational ages and determine what factors increase or decrease their likelihood of survival with or without a major developmental disability (e.g. intellectual disability, cerebral palsy and autism). This will allow us to explore the impact of changes in antenatal and perinatal care on these important pathways. As well as measuring the contribution of preterm birth to developmental disabilities, we also plan to measure the later hospitalisation experience of children born at different gestational ages and with different developmental disabilities. This will provide the basis for economic analyses of the costs associated with preterm birth and with specific developmental disabilities.

Funders of the project: NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

THE TRANSITION FROM SECONDARY SCHOOL TO ADULTHOOD: EXPERIENCES AND LIFE OUTCOMES FOR YOUTH WITH AN INTELLECTUAL DISABILITY AND THEIR FAMILIES

Helen Leonard, Carol Bower, Nick de Klerk, Gwynnyth Llewellyn, Stewart Einfeld, Trevor Parmenter, Vivienne Riches, Bruce Tonge, Nick Lennox, Ron Chalmers, John Brigg, Greg Lewis, Jackie Softly, Jenny Bourke, Paula Dyke, Kitty Foley, Katherine Bathgate, Terri Pikora, Sonya Girdler, Lyn McPherson.

This ARC Linkage project, which developed from an ARACY Seed-funding grant, seeks to explore the challenges faced and outcomes achieved by young people with an intellectual disability as they move from secondary school into adult life. There are likely to be major life changes for these young people as they move into adulthood with respect to work, where they live, who cares for them, how their health and therapy needs are managed and how they spend their days. The study is investigating the factors at an individual, educational, family, and societal level which contribute positively and negatively to a 'good' outcome for the young person and their family.

This study involves young people with intellectual disability aged 16 years and over from four separate sources: i) Down syndrome NOW cohort in WA, (ii) the Queensland Centre for Intellectual and Developmental Disability's ASK study (a five year project aiming to improve the health of young people with intellectual disability); (iii) the Australian Child to Adult Development (ACAD) Study at the University of Sydney and (iv) the Australia-wide Rett syndrome cohort. We used the World Health Organization's International Classification of Functioning, Disability and Health (ICF) framework to take into account the many issues which may affect a person's participation in all aspects of life.

In 2009/10 questionnaires were administered to 269 families of young people with Down syndrome in Western Australia. Of the 203 (75.0%) returned, 164 (80.8%) had left school with ages varying from pre-transition (16-17 years), early transition (18-20 years) to late transition (23-31 years). Follow-up questionnaires were administered in 2011/2012 to 229 families with 197(86%) families responding.

In consultation with the WA research team the Queensland group administered a similar questionnaire to the parents of the young people, aged between 17 and 23 years, in the Queensland ASK cohort, with 150 (59%) respondents. We are currently comparing the transition experiences of the young people and their families in the WA and Queensland cohorts. Using the existing ACAD data previously collected in New South Wales and Victoria we are comparing the behavior of individuals with Down syndrome using both the WA and ACAD cohorts, with young people with intellectual disability of other cause in the ACAD cohort.

Based on the 2009 Down Syndrome NOW data, among those who had left school (n=164) the most common main day occupation was sheltered employment (39.0%), followed by open employment (25.6%) and alternatives to employment (ATE) (25.0%) while the remainder (10.4%) attended training. Not unexpectedly young adults who were reported as functioning better within self-care, community and communication skills were more likely to be participating in open employment or training than those in sheltered employment or alternatives to employment. However we did not find any evidence that poor health status adversely impacted on workplace participation. Similarly, families of young people with Down syndrome attending open employment reported better quality of life than families of young people attending sheltered employment. The young person's behaviour had a weak association with family quality of life.

Using the data from three time-points in 2004, 2009 and 2011 we looked at the trajectory of behavior in young people by age. We found that whilst the disruptive, self-absorbed, communication disturbance and anxiety components of behavior improved with age, the social-relating problems and depressive symptoms persisted. These findings contribute to the understanding of mental health status across the developmental time periods in people with Down syndrome. We also examined the changes in behavior over time for young people according to their day occupation. We found that participation in open employment was associated with an improvement in behaviour from 2009 to 2011 compared to those in other day occupations.

The social participation of young adults with Down syndrome from a parental perspective and its relationship with the physical and social environment was explored. Young people were found to have more difficulty participating in social roles (e.g. relationships, community life, recreation etc.) than they did participating in daily activities (e.g. personal care, communication, housing etc.). The most commonly reported barriers to participation were negative attitudes of strangers, and lack of support from friends, availability of jobs and public transport.

We also conducted a qualitative study to investigate the experiences of mothers of young adults with either Down syndrome or Rett syndrome who were transitioning from secondary school to adult life. In contrast with Rett syndrome, mothers of young adults with Down syndrome described more difficult pathways to attaining stability in adult roles. The facilitators and barriers which emerged were in the area of support, relationships, services, systems and policies. The study highlighted the unwavering commitment of parents to their son or daughter with an intellectual disability and the extraordinary resourcefulness of many families in their quest to ensure that their son's or daughter's quality of life is maximised.

Alcohol & Pregnancy & FASD Research Group

2013 was an important year for disseminating and translating information from recently completed projects. Members of the Alcohol & Pregnancy & FASD Research Group were involved as organisers and presenters at the first Australasian FASD Conference 'A time to learn, a time to act' and also made seven presentations at the 5th International FASD Conference in Vancouver Canada. These included topics such as the Marulu Strategy; the development of a diagnostic instrument for FASD in Australia; alcohol and pregnancy and the disparity between women's expectations and health professionals' practice; evaluation of FASD information and services for foster carers; and FASD knowledge, attitudes and practice of WA justice professionals. We also participated, by invitation, in a workshop at the Vancouver Conference to harmonise the diagnosis of FASD internationally. A further 30 presentations were made at other national and local conferences, seminars and workshops.

We were successful in obtaining a $1.4M grant from the National Health and Medical Research Council (NHMRC) to assess how many juvenile offenders in detention are affected by FASD. The funding will allow researchers to determine how common FASD are in young people in detention, develop a FASD screening tool appropriate for young people entering the juvenile justice system, and develop appropriate management strategies for these young people. The study is significant and will contribute important findings, as little is known about the prevalence of FASD either in the general community or among high risk groups. We also received a grant from the Department of the Attorney General Criminal Property Confiscation Grants Program to develop resources about understanding FASD for justice professionals. These projects build on previous Telethon Kids Institute research on FASD in the justice system and the overwhelming need for more information and services.

The Telethon Kids Institute started working with the Fitzroy Valley community to develop a prevention strategy with the bold goal to "Make FASD History" by driving down rates of drinking in pregnancy. The first phase will focus on the design of the FASD Prevention Strategy including community consultation and the development and pre-testing of the communication campaign materials. This project is funded by the Western Australian Government Department of Aboriginal Affairs and philanthropic funding from the McCusker Foundation.

Alcohol and pregnancy and fetal alcohol spectrum disorders

ALCOHOL AND PREGNANCY AND FETAL ALCOHOL SPECTRUM DISORDER: MIDWIVES' KNOWLEDGE, ATTITUDES AND PRACTICE

Dr Jan Payne, Dr Rochelle Watkins, Ms Heather Jones, Dr Tracy Reibel, Dr Raewyn Mutch, Dr Amanda Wilkins, Ms Julie Whitlock, Winthrop Research Professor Carol Bower

The aim of this research was to describe the knowledge, attitudes and practice of midwives employed in the Western Australian Country Health Services (WACHS) in relation to alcohol consumption in pregnancy and Fetal Alcohol Spectrum Disorders (FASD).

The research was conducted in collaboration with WACHS, and stakeholders from the Department of Health WA, Australian College of Midwives (WA Branch) Inc, Curtin University and King Edward Memorial Hospital for Women. A steering group was formed comprising seven researchers and one community representative. A midwifery reference group advised the project and provided expert opinion.

Data were collected during June and July 2013 from midwifery managers from the 19 WACHS maternity sites across the seven health regions in country WA. Descriptive statistics have been produced and we are currently conducting further in-depth analysis.

Funding: This project was supported by the NHMRC Program Grant 572742 and Research Fellowship 634341

THE DEVELOPMENT OF A DIAGNOSTIC INSTRUMENT FOR FASD IN AUSTRALIA

Australian FASD Collaboration, including Professor Carol Bower as a lead investigator; Dr Rochelle Watkins, Dr Jan Payne, Dr Raewyn Mutch, Dr Amanda Wilkins, Dr James Fitzpatrick, Ms Heather Jones

We conducted a literature review of Australian and international literature on screening and diagnosis of FASD; held community conversations with women in Perth and Cairns to explore questions about alcohol and pregnancy; conducted a Delphi survey with Australian and international health professionals

and researchers with expertise in FASD to identify key components for the diagnostic instrument; and held a consensus development workshop to consider all this evidence and make recommendations for the content of the diagnostic instrument and methods to validate the instrument and support its use. Five papers based on this work have been published and a sixth has been submitted.

Funding: This project was funded by the Commonwealth Department of Health; NHMRC Program Grant 572742, NHMRC Fellowship 634341

Dissemination:

Publications

1. Recommendations from a consensus development workshop on the diagnosis of fetal alcohol spectrum disorders in Australia. BMC Pediatrics 2013.13:156
2. Involving consumers and the community in the development of a diagnostic instrument for fetal alcohol spectrum disorders in Australia. Health Research Policy and Systems.2013, 11:26.
3. Delphi study of screening for fetal alcohol spectrum disorders in Australia. BMC Pediatr 2013, 13:13.
4. Consensus diagnostic criteria for fetal alcohol spectrum disorders in Australia: a modified Delphi study. BMJ Open. 2012 Oct 25;2(5). doi:pii: e001918.10.1136.
5. Health professionals' perceptions about the adoption of existing guidelines for the diagnosis of fetal alcohol spectrum disorders in Australia. BMC Pediatr. 2012 Jun 14;12(1):69.

Presentations

1. Australasian FASD Conference 'A time to learn, a time to act' Brisbane Australia
2. 5th International FASD Conference in Vancouver Canada

FASD: KNOWLEDGE, ATTITUDES AND PRACTICE IN THE WA JUSTICE SYSTEM

Dr Raewyn Mutch, Dr Rochelle Watkins, Ms Heather Jones, Professor Carol Bower

Researchers wanted to assess justice professionals' awareness and knowledge of FASD; assess the perceived impact of FASD on their practice; and identify their FASD information needs. We conducted an on-line survey of staff across the four sectors of the Western Australian justice system – judicial officers, lawyers, corrective services officers and WA Police.

Funding: This project was funded by the Foundation for Alcohol Research and Education.

Dissemination:

Publication

Final Report available from the Alcohol, Pregnancy and FASD website

Presentations

1. Australasian FASD Conference 'A time to learn, a time to act' Brisbane Australia
2. 5th International FASD Conference in Vancouver Canada
3. Seminars with WA justice professionals, including Heads of Jurisdiction, Childrens Court magistrates, District Court magistrates, Department of Corrective Services

Translation: Since the completion of the 'FASD: Knowledge, attitudes and practice in the WA justice system' project and publication of the final report we have:

- met with judges, magistrates and lawyers to plan educational opportunities and continuing professional development
- made presentations at judicial and legal conferences and seminars
- met with judicial officers to discuss the establishment of assessment and diagnostic facilities

This has resulted in:

- invitation to update the FASD section in Chapter 4 Disabilities in the WA Equality before the Law Bench Book
- invitations to present at legal and judicial conferences in 2014 – working in collaboration with lawyers and magistrates to explain how FASD affects a child's development and abilities, how these may present and implications for people working in the justice system
- successful NHMRC grant application to evaluate the need for, feasibility and effectiveness of two interventions to improve the identification and management of youth with FASD in the justice system
- successful grant application to develop on-line learning education packages, short videos and resources for justice professionals

EVALUATING INFORMATION AND SERVICES FOR PARENTS AND CARERS OF CHILDREN LIVING WITH FASD

Dr Amanda Wilkins, Ms Heather Jones, Dr Rochelle Watkins, Professor Carol Bower

The purpose of the study was to find out what FASD information and resources were available to parents and carers, were these useful, what were the parents' and carers' specific needs with respect to information and resources to support them raising a child with FASD.

We conducted:

- 3 focus groups with a total of 26 foster carers in the metropolitan area and a regional centre
- a face to face interview with one foster carer in the metropolitan area
- a paper-based survey of foster carers to evaluate the information and resources they had accessed with input from 10 foster carers
- a review of accessible paper-based, audio-visual and electronic resources specific to Australia

Funding: This project was funded by the Foundation for Alcohol Research and Education.

Dissemination:

Publications

Final Report available from the Alcohol, Pregnancy and FASD website

Presentations

1. Australasian FASD Conference 'A time to learn, a time to act' Brisbane Australia

Translation:

Since the completion of this project we have conducted:

- 2 interactive workshops in the metropolitan area and regional centre with 17 foster carers attending. Carers' response to the workshops was overwhelmingly positive with participants commenting in the evaluation that it was great to listen to real life stories and gain practical strategies for managing children living with FASD.
- 2 workshops with staff from the Department for Child Protection, with 97% indicating that it was useful and practical, and relevant to their work with children and families.

We also sponsored 2 foster carers to attend the Australasian FASD Conference. These carers will be able to share their knowledge and practical experiences and strategies with other carers.

ASSISTED REPRODUCTIVE TECHNOLOGY AND BIRTH DEFECTS

Michele Hansen, Jennifer Kurinczuk, Nicholas de Klerk, Peter Burton, Elizabeth Milne and Carol Bower

In Australia, 1 in 25 births are conceived using Assisted Reproductive Technologies such as IVF and this figure is expected to rise. The use of IVF is increasing worldwide, with an annual increase in treatment cycles of 5-10% over the last decade in developed countries. The statutory Western Australian (WA) Reproductive Technology Register (RTR) was established to monitor the safety of Assisted Reproductive Technology (ART) procedures for the women undergoing treatment in WA and any children born. In 2012 we published a large population-based data linkage study examining birth defect prevalence in ART children compared with all other WA-born children (1994-2002). We found that birth defect prevalence had decreased over time in ART children and that the data items available for analysis on the RTR (number of embryos transferred, type of ART, fresh or frozen transfer) could not explain this decline. The type of embryo culture media used in an ART treatment cycle is not recorded on the RTR or similar registers worldwide and there is recent interest and controversy in the literature on the potential impact of different culture media on birthweight and fetal growth but no information on birth defects. We obtained a small seed grant from the Telethon Kids Institute to undertake a preliminary study assessing whether changes in embryo culture media over time could explain some of the decline in birth defect prevalence in WA ART infants. The two largest clinics operating during our initial study period have agreed to collaborate with us and provide information about changes in laboratory practices at their clinics during the study period. We expect to complete data analyses and publish the results of this preliminary study in 2014.

The decline in birth defect prevalence in WA ART infants and a more detailed analysis of the severe defects of blastogenesis occurring in the first 4 weeks of gestation were presented at the national Fertility Society of Australia meeting in September 2013.

We were invited to publish a systematic review of the ART and birth defects literature by the Editors of Human Reproduction Update, the top journal in this field. The review updated our previous systematic review and meta-analysis of the ART and birth defects literature, published in 2005. There were 45 cohort studies included in the review. ART infants (n=92 671) had a higher risk of birth defects (RR 1.3; 95% CI 1.2-1.4) compared with naturally conceived infants (n= 3 870 760). The risk further increased when data were restricted to major birth defects (RR 1.4, 95% CI 1.3-1.6) or singletons only (RR 1.4, 95% CI 1.3-1.4). The results for ART multiples were less clear. When all data for multiples were pooled the RR estimate was 1.1 (95% CI 1.0-1.1) but this increased to 1.3 (95% CI 1.0-1.6) when the analysis was restricted to studies of ART twins where some adjustment was made for differences in zygosity distribution between ART and non-ART multiples. These data are important for the counselling of prospective ART patients.

We also collaborated with Dr Georgina Chambers and colleagues at the National Perinatal Epidemiology and Statistics Unit to perform an economic evaluation of hospital admission in ART singletons in the first 5 years of life. The study compared hospital utilization and costs for all singleton babies born in WA between 1994 and 2003; 222 425 non-ART singletons and 2199 ART conceived singletons. ART singletons stayed longer in hospital at birth and were 20% more likely to be admitted to hospital during the first 5 years of life. The average adjusted difference in hospital admission costs up to 5 years of age was $2490, with most of the additional cost occurring during the birth-admission ($1473). Clinicians and patients should be aware of the risk of poorer perinatal outcomes and increased hospitalization of ART singletons compared with non-ART singletons. These differences are significant enough to affect health-care resource consumption, but are substantially less than those associated with ART multiple birth infants. The results of this study were presented by Dr Chambers at the European Society for Human Reproduction and Embryology conference in London, July 2013 and have recently been published in the journal Human Reproduction.

1 in 25 children in Australia are conceived using Assisted Reproductive Technologies like in vitro fertilisation (IVF) and this figure rises to 1 in 7 for women over 37 years of age. We are comparing the health of these children to the health of other children conceived without these technologies (naturally conceived). For example, we are looking at whether children conceived following ART treatment are more likely than other children to be admitted to hospital, have birth defects, an intellectual disability or cerebral palsy.

Funding: NHMRC Project Grant #211930; NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB).

Collaboration for Applied Research and Evaluation

The Collaboration for Applied Research and Evaluation was established by the Telethon Institute in 2000 to progress the translation of research into policy and practice and to conduct high quality policy and practice relevant research based on the priorities of the Health System.

The mission of the Collaboration is to conduct research and provide relevant analysis and interpretation of research information to facilitate evidence based planning, policy and practice to optimise maternal, child and youth health outcomes in Western Australia

The role of the Collaboration is to provide services for health related policy research and development, and program development and evaluation. Those working in the Collaboration have an understanding of issues on both sides of the research to policy and practice continuum. Several of the team have worked in or within government program development and in service delivery areas, others have extensive experience in specific areas of specialisation in practice and research in areas including maternal health, child development, Aboriginal and community development.

Women and Newborns

A STUDY EXAMINING POST NATAL FOLLOW-UP OF WOMEN RECEIVING PREGNANCY CARE WITH THE WOMEN AND NEWBORN DRUG AND ALCOHOL SERVICE (WANDAS)

Anna Fletcher (Telethon Institute), Angela O'Connor (Women's and Newborns Alcohol and Drug Service, King Edward Memorial Hospital), Renate McLaurin (Women's and Newborns Alcohol and Drug Service, King Edward Memorial Hospital)

This study aims to inform further development of WANDAS to better facilitate the transition of patient care from the tertiary environment into the community post-birth. To inform this development the study endeavours to describe the experiences of those who attended WANDAS during their pregnancy, and to identify possible barriers and enablers to accessing care during the postnatal period. Consultation with health and support services will provide information on the barriers and enablers to engaging with WANDAS patients which, together with the patient perspective, will help to inform the recommendations for service improvement. This project will be completed by October 2014.

Funders of the project: Department of Health

MATCH STUDY: PRAGMATIC RANDOMIZED CONTROLLED STUDY ON MATERNITY MODELS OF CARE

Tanyana Jackiewicz (Telethon Institute), Karen Ogilvie (Kaleey a Hospital, South Metropolitan Health Service), Kerryl Spence (Kaleeya Hospital, South Metropolitan Health Service)

This project has stalled indefinitely due to funding decisions out of the control of the Telethon Institute for Child Health Research.

Funders of the project: Department of Health

STRONG SPIRIT STRONG FUTURES EVALUATION

Dr Tracy Reibel and Ms Kaashifah Bruce (Telethon Institute), Michelle Grey (Drug and Alcohol Authority)

The Drug and Alcohol Office (DAO) state-wide Aboriginal fetal alcohol spectrum disorder (FASD) Prevention Program received funding of $2.23 million, over four years, to develop a suite of Aboriginal FASD prevention initiatives. The Strong Spirit Strong Future (SSSF) - Promoting Healthy Women and Pregnancies project commenced in July 2010, and included the development of culturally secure resources, workforce development initiatives and community awareness campaigns. The project aimed to improve the ability of a range of service providers to respond to issues of alcohol and pregnancy with Aboriginal people, families, and communities through culturally secure resources, awareness raising and workforce development. This research project will describe the underpinning theory and logic (Principles) of the SSSF Project, matching these to what was actually done and how this was interpreted by stakeholders. This project is expected to be completed by the end of April 2014.

Funders of the project: Department of Health

ESSENTIAL ELEMENTS OF GOOD ANTENATAL CARE: THE VOICES OF YOUNG ABORIGINAL WOMEN

Dr Tracy Reibel (Telethon Institute), Lli Chapman (Aboriginal Maternity Services Support Unit, Women and Newborns Health Service (AMSSU)), Denese Griffin (AMSSU), Margaret Davies (King Edward Memorial Hospital (KEMH)

This project is being conducted as part of the Aboriginal Maternity Support Services Unit's strategic development to form a comprehensive understanding of what is likely to encourage young pregnant Aboriginal women to access antenatal services. Specific consultation with young (<20 years) pregnant Aboriginal women will be undertaken across the State to explore their views on pregnancy care. This project will be completed by the end of April 2014.

Funders of the project: Department of Health

AMSSU JOURNEY'S PROJECT

Dr Paula Wyndow and Tanyana Jackiewicz (Telethon Institute), Lli Chapman (AMSSU)

Denese Griffin (AMSSU)

The aim of this research project is to determine the feasibility of a practical and realistic across agency pathway model of care that supports pregnant Aboriginal women and their families through a system of services. The project requires the identification of key organisations and individuals who are involved in the patient journey of pregnant Aboriginal women. Maps will be developed to reflect four main groups of organisations that are involved in supporting Aboriginal women during pregnancy; these include the Health Department of Western Australia, Aboriginal Medical Services, other non-government health organisations, and non-health community organisations/agencies. Consultation with agencies involved in supporting pregnant Aboriginal women will be undertaken statewide through focus groups and one on one interviews. This project is expected to be completed by June 2014.

Funders of the project: Department of Health

MATERNAL SATISFACTION WITH PUBLIC MATERNITY SERVICES IN WA (ALSO KNOWN AS WOMEN'S SATISFACTION WITH THEIR MATERNITY CARE)

Dr Kim Clark and Dr Tracy Reibel (Telethon Institute), Terri Barrett (Statewide Obstetric Services Unit)

The aims of the project are to develop and pilot a theoretically-framed survey tool for use in monitoring and evaluating women's satisfaction with maternity services. This research project is now complete and has produced a valid and reliable service evaluation instrument that is capable of aiding the Statewide Obstetric Support Unit in its role of providing quality guidance on maternity models of care across the State.

Funders of the project: Department of Health

THE DEVELOPMENT OF A NOVEL ANTENATAL EDUCATION PROGRAMME FOR OBESE MOTHERS-TO-BE ON THEIR INTENTION TO MANAGE THEIR GESTATIONAL WEIGHT GAIN AND FOSTER A HEALTHY LIFESTYLE

Anna Fletcher, Dr Lisa Gibson and Tanyana Jackiewicz (Telethon Institute), Professor Yvonne Hauck (KEMH)

The aim of this project is to develop an evidence-based and field-tested antenatal care and education package based on the 'Centering Pregnancy' model, that is acceptable to pregnant women with a body mass index (BMI) of ≥30 kg/m2. The package is to be designed with the goal of positively influencing participants' intention to manage and thus minimise their gestational weight gain whilst fostering the adoption of a healthy lifestyle.

This project was completed in September 2013 and the major output is the Blooming Together

Program; an eight-session, group-delivered, multi-disciplinary model of care incorporating continuity of care and behavioural change strategies to achieve a healthy pregnancy. This Program is ready to be trialed in the field.

Funders of the project: Department of Health

Child and Youth

EVALUATION OF THE INTEGRATED SERVICE INITIATIVES TARGETING THE EARLY YEARS IN WESTERN AUSTRALIA

Dr Kim Clark and Rhonda Breen (Telethon Institute), Sue Kiely (Child Adolescent Community Health, Child Adolescent Health Service)

This project will explore the provision of children's services in communities, assess how these services work together and evaluate their resulting impact on children's social, emotional and academic functioning across the early years through to early primary (0-8 years). The study will provide insights into how integrated networks can be evaluated and the impact of an integrated approach to service on families' and children's functioning. The study hypothesis is that higher levels of local education, health, and community service integration lead to higher levels of parent and teacher and other service provider role satisfaction and lower levels of developmental vulnerability among children in their first year of full-time schooling living in the lowest SES quintile of school areas in WA. This project is expected to be completed by the end of 2014.

Funders of the project: Department of Health

EVALUATION OF THE CHOICE AND PARTNERSHIP APPROACH (CAPA) WITHIN CHILD AND ADOLESCENT MENTAL HEALTH SERVICES

Dr Kim Clark (Telethon Institute), Keren Geddes (Child Adolescent Mental Health (CAMHS))

The aim of this project is to conduct a comprehensive evaluation of CAPA across the two trial sites in the Perth Metropolitan Area. The evaluation will consist of both process and outcome/impact components. The results of the process evaluation will provide valuable information that other CAMHS sites across WA and Australia, and internationally, can use to inform the successful implementation of CAPA whilst reducing disruption to the service. It may also indicate those aspects of the model that are 'successful' and those that are problematic; potentially allowing the development of a more refined model of service delivery for WA CAMHS. This project will be completed by the beginning of 2015.

Funders of the project: Department of Health

ANAEMIA IN WESTERN AUSTRALIA: INCIDENCE IN ABORIGINAL AND NON-ABORIGINAL POPULATIONS ACROSS THE STATE

Grant Smith (Telethon Institute), Professor Karen Edmund (Princess Margaret Hospital (PMH))

The major aim of this study is to use existing full blood count data to identify diagnoses of moderate to severe anaemia in children across Western Australia. Differences across subpopulations of the state will be examined to identify risk factors for anaemia and identify significant differences across Western Australian communities (particularly remote/rural Aboriginal communities). Where possible, incidence rates of various subtypes of anaemia will be also be examined. This project is expected to be completed by the beginning of 2015.

Funders of the project: Department of Health

AUSTRALIAN PAEDIATRIC ADHD STUDY: A PILOT

Grant Smith (Telethon Institute), Dr Brad Jongeling (Child Development Service, Child Adolescent Health Service), Dr John Wray Child Development Service, Child Adolescent Health Service)

The primary aim of this pilot study is to assess the methods proposed for the prospective longitudinal study into ADHD diagnosis and treatment in Australia. A successful pilot will allow for funding to be sought for a large-scale prospective study into the diagnosis and treatment of ADHD in Australia. This project is due for completion in May 2014.

Funders of the project: Department of Health

RAINE ADHD STUDY 17 YEAR FOLLOW-UP: LONG-TERM OUTCOMES ASSOCIATED WITH THE USE OF STIMULANT MEDICATION IN THE TREATMENT OF ADHD: OUTCOMES AT 17 YEARS OF AGE

Grant Smith (Telethon Institute), Craig Russell (Child Adolescent Mental Health Service) and Ministerial Implementation Committee on ADHD (MICADHD)

This project replicates the methodology used in the 2010 report: Raine ADHD Study: Long-term outcomes associated with stimulant medication in the treatment of ADHD in children. However, where the previous report examined outcomes measured at the 14-years of age, this project will examine outcomes measured at 17 years of age. This final report for this project has been completed.

Funders of the project: Department of Health

TRIPLE-P PARENTING PROGRAM: LONG-TERM OUTCOMES AND ECONOMIC BENEFITS

Grant Smith (Telethon Institute)

This research project will evaluate the Triple-P Program's long term effectiveness, using data collected in the initial effectiveness trial and data on the children and their family up to 13 years following the intervention (children of parents enrolled in the program are now at least 16 years old). The WA Triple-P study database will be linked to a number of administrative databases (e.g. education, health, mental health, justice, child protection, drug and alcohol, mortality) to determine whether the program was associated with better long-term outcomes for children.

This project is expected to be completed by April 2014.

Funders of the project: Department of Health

Breathing for Life Study

RESPIRATORY SYMPTOMS IN CHILDREN AND YOUNG ADULTS WITH CEREBRAL PALSY

Dr Eve Blair (Telethon Institute), Dr Andrew Wilson (PMH), Dr Marie Blackmore, Research Coordinator, The Centre for Cerebral Palsy

The aim of this study is to determine the prevalence of respiratory problems in children and adults with CP in Western Australia. This information will be used to identify and intervene as early as possible in order to prevent serious respiratory problems from developing. This study was completed in September 2013.

Funders of the project: Department of Health

Childhood Cancer

AUSTRALIAN STUDY OF CAUSES OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN

Elizabeth Milne, Carol Bower, Nick de Klerk, Ursula Kees, in collaboration with Bruce Armstrong, Frank van Bockxmeer, Michelle Haber, Rodney Scott, John Attia, Murray Norris, Lin Fritschi, Margaret Miller, Judith Thompson, Frank Alvaro, Catherine Cole, Luciano Dalla Pozza, John Daubenton, Peter Downie, Marie Kirby, Liane Lockwood, Glenn Marshall, Elizabeth Smibert, Ram Suppiah .

Researchers in the Childhood Cancer Epidemiology program have been analysing the data collected between 2003 and 2007 in this national case-control study of the causes of childhood acute lymphoblastic leukaemia (ALL). The primary hypothesis of this study was that maternal folate supplementation during pregnancy protects against ALL in the offspring, with the effect modified by genetic factors in folate metabolism.

The following papers using data from this study were published in 2013:

Metayer C, Milne E, Clavel J, et al. The Childhood Leukemia International Consortium. Cancer Epidemiology. 2013;37:336-47.

This paper describes an international consortium of leukemia studies, in which Professor Milne takes a leading role, and for which Aus-ALL was one of the founding participant studies.

Milne E, Greenop K, Armstrong BK, Buffler P et al. An international meta-analysis of the association between fetal growth and risk of childhood acute lymphoblastic leukemia – a report from the Childhood Leukemia International Consortium (CLIC). International Journal of Cancer 2013; 133: 2968-79.

This paper describes the results of the first pooled analysis to be undertaken under the auspices of CLIC. These results, showing a modest increased risk of ALL among babies born with greater than expected birth weight, support the previously reported findings from Aus-ALL.

Analysis is also under way to examine whether there are links between risk of ALL and infant nutrition, and variations in genes that influence the way the body processes food and chemicals

Funders of the project: NHMRC Grant #254539, and Cancer Council WA.

NATIONAL CASE-CONTROL STUDY OF THE CAUSES OF CHILDHOOD BRAIN TUMOURS

Elizabeth Milne, Carol Bower, Nick de Klerk, Peter Dallas, in collaboration with Bruce Armstrong, Frank van Bockxmeer, Rodney Scott, John Attia, Lin Fritschi, David Ashley, Lesley Ashton, Judith Thompson, Murray Norris , Richard Cohn, Margaret Miller, Luce dalla Pozza, John Daubenton, Timothy Hassall, Maria Kirby, Stewart Kellie, Ross Pinkerton, Frank Alvaro, Angela Alessandri.

The Australian Study of Childhood Brain Tumours (AUS-CBT) was a national case-control study into the causes of childhood brain tumours (CBT). It aimed to investigate genetic, dietary and environmental risk factors for CBT, and is the sister study to the Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (AUS-ALL). The study recruited case and control families between 2006 and 2010; data collection was completed in 2011.

The study involved children aged 0-14 years. Case children and their parents were recruited from the nine paediatric oncology units nationwide. In total, we were notified of 734 eligible cases, of whom 568 were invited (77%) to participate and 374 consented, with 335 providing either self-administered questionnaires or doing short telephone interviews to provide demographic and basic exposure data. 302 case families returned full exposure questionnaires, and 295 did a food frequency questionnaire. We received DNA samples from 355 families for genotyping, which is complete. A total of 194 families declined to participate or could not be re-contacted, and a further 162 were not invited due to medical or psychosocial reasons.

Control children (that is, children without a brain tumour) and their families were recruited through national random digit dialing and frequency matched to the case children by age, sex and State of residence. A total of 1363 controls were recruited. We received exposure questionnaires from 941 control families, food frequency questionnaires from 726 control families and DNA samples from 974 control families for genotyping, which is complete.

The following papers were published in 2013:

Milne E, Greenop K, Scott RJ, Bower CI, Miller M, Ashton L, Heath J, de Klerk NH, Armstrong BK. Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors Cancer Causes and Control. 2013; 24(2): 391-402

In this paper, re report U-shaped associations between paternal alcohol consumption in the year before the pregnancy and both types of cancer, and an increased risk of CBT – but not ALL – associated with a moderate intake of spirits by fathers during this period.

Greenop K R, Peters S, Bailey HD, Fritschi L, Attia J, Scott RJ, Glass DC, de Klerk NH, Alvaro F, Armstrong BK Milne E. Exposure to pesticides and the risk of childhood brain tumors. Cancer Causes Control 2013. doi:10.1007/s10552-013-0205-1.

This paper reports our findings that pesticide use in the home in the year leading up to conception, as well as during the pregnancy, is associated with an increased risk of brain tumours in the offspring.

Milne E, Greenop K, Scott RJ, Ashton L, Cohn R, de Klerk NH, Armstrong BK. Parental prenatal smoking and risk of childhood brain tumours: Results from the Australian Study of Childhood Brain Tumors International Journal of Cancer 2013;133:253-60.

In this paper, we report that we found little association between parental smoking and risk of childhood brain tumours overall; however, the risks for maternal smoking before and during pregnancy appeared to be elevated among children diagnosed before 2 years of age.

Peters S, Glass DC, Reid A, de Klerk N, Armstrong BK, Kellie S, Ashton LJ, Milne E, Fritschi L Parental occupational exposure to engine exhausts and childhood brain tumors. International Journal of Cancer. 2013;132:2975-9.

This paper reports our findings that parental occupational exposure to diesel exhaust before the pregnancy may increase the risk of brain tumours in the offspring.

Heiden T, Bailey HD, Armstrong BK, Milne E. Differential participation among cases in epidemiological studies of childhood cancers. BMC Research Notes, 2013; 6:191. doi: 10.1186/1756-0500-6-191.

This paper describes differences in participation in epidemiological studies of childhood cancers related to the timing and method of approach to parents.

Analysis and manuscript preparation are under

way to examine whether there are links between risk of CBT and:

- Maternal coffee consumption
- Parental refueling of vehicles and use of wood burners in the home
- Variations in genes that influence the way the body processes food and chemicals

Funders of the project: NHMRC Grant #404089.

NUTRITION AND GENOME HEALTH IN CHILDREN

Elizabeth Milne, Michael Fenech, Bruce Armstrong, Nick de Klerk, Margaret Miller.

The Nutrition and Genome Health in Children Study aimed to identify key nutritional and genetic factors associated with DNA damage in children. It aimed to describe the nature of the interaction between nutritional and genetic factors in determining level of DNA damage in children, and also the associations between body mass index, DNA damage and micronutrient levels in children.

This study was a cross-sectional study of 450 Western Australian children, conducted between 2009 and 2011. Participants were children aged 3, 6 or 9 years at recruitment who had never been diagnosed with asthma, diabetes, cancer, arthritis or epilepsy. Participants and their parents were recruited via primary schools, posters displays and flyers, advertisements in local newspapers and information letters distributed to a wide range of organizations. These include crèches, day care centres, playgroups, sports centres and libraries.

The child's diet and macro- and micro-nutrient intake was assessed using parent-completed Food Frequency Questionnaires (FFQs). A sample of the child's blood was taken and used to assess micronutrient levels and specific biomarkers of DNA damage. The blood sample was also used to identify genetic polymorphisms related to nutrient metabolism and DNA repair. Saliva samples collected from the child were used to measure cortisol and cotinine levels, as indicators of psychological stress and exposure to environmental tobacco smoke, respectively. Parents were given feedback on their child's diet, and dietary advice was provided by a dietitian where needed.

In all, 464 participants provided data. Statistical analysis of these data is currently in progress, and the following papers are in preparation.

- Association between children's sun exposure and plasma Vitamin D
- Association between children's plasma micronutrients and telomere length
- Association between children's plasma micronutrients and markers of DNA damage

Funders of the project: NHMRC Grant#572623.

Childhood Cancer Epidemiology: other work

Neale RE, Stiller CA, Bunch KJ, Milne E, Mineau GP, Murphy MFG. Familial Aggregation of Childhood and Adult Cancer in the Utah Genealogy. International Journal of Cancer. 2013; 133: 2953-60.

This paper reports our findings that mothers and siblings of children with cancer had a higher risk of cancer in adulthood than those of children without cancer, and that this association appeared to be stronger among relatives of cases diagnosed before 5 years of age.

Hansen M, Kurinczuk J, Milne E, de Klerk NH, Bower CI. Assisted reproductive technology and birth defects – a systematic review and meta-analysis. Human Reproduction Update, 2013. doi:10.1093/humupd/dmt006

In this paper, we describe how we combined data from 45 studies and found a consistent increase in risk of birth defects among children born as a result of assisted reproductive technology.

Telethon Kids Institute (Adelaide Team) and the Fraser Mustard Centre

At the Telethon Kids Institute (Adelaide Team), a key component of our work continues to include the Australian Early Development Index (AEDI) research program, an Australian Government backed commitment that measures children's development in communities across the nation. The AEDI is a population measure of how our children develop through to their early school years. Teachers collect data across core areas of learning, health and wellbeing and this data is used to develop a snapshot of child development in communities across the nation.

Another primary aspect of the Adelaide Team is the "Fraser Mustard Centre", established in September 2012 and named in recognition of Dr Fraser Mustard's contribution to South Australia. The Telethon Kids Institute has joined forces with the SA Department for Education and Child Development to create a research partnership aimed at improving developmental, health and educational outcomes for children and young people. The Fraser Mustard Centre has been created to bring together leading Australian child researchers and innovative government policy makers and planners with a focus on enhancing programs and services for young people.

In 2013, the Fraser Mustard Centre continued to develop its research activities and linkages across the SA Department for Education and Child Development, notably expanding its evaluation activities from one initial evaluation of Children's Centres to now being involved in or leading the evaluation of five Government programs and initiatives.

Whilst much of the work of the Fraser Mustard Centre is in the early stages, a few early examples of the successes of the Fraser Mustard Centre include:

Measurement of the wellbeing of approximately 6,500 children in the middle years of school. This is a pilot project to inform a state-wide census measure, which proposes to measure the wellbeing of around 60,000 children over the next three years. The Middle Years Development Instrument (MDI) recently received additional financial support through an ARC Linkage grant of $223,000 for 2013-2015.

Identification of gaps in service data collections in a flagship early childhood program in South Australia (South Australian Children's Centres), and subsequent support to the Department to progress a project to enhance data collections in Children's Centres. Enhanced data collections will better enable the Department to evaluate the reach and impact of these flagship services. Our advocacy and strategic advice to DECD has enabled the Children's Centre project team to gain the support of Department Executives and data system custodians and thus the enhancement project has been advanced within DECD and is now being scheduled for development.

Development, education, health and wellbeing of children and young people

AUSTRALIAN EARLY DEVELOPMENT INDEX (AEDI)

Sally Brinkman, Tess Gregory

Project support: Angela Kinnell, Alanna Sincovich

The Australian Early Development Index (AEDI) is a population measure of young children's development. Like a census, it involves collecting information to help create a snapshot of children's development in communities across Australia. Teachers complete the checklist for children in their first year of full-time schooling. The AEDI measures five developmental domains:

- Physical health and wellbeing
- Social competence
- Emotional maturity
- Language and cognitive skills (school-based)
- Communication skills and general knowledge

In 2009, the AEDI was completed nationwide for the first time with the Australian Government providing $21.9 million for the implementation of the AEDI in recognition of the need for all communities to have information about early childhood development. In 2009, information was collected on 261,203 children (97.5 per cent of the estimated national five-year-old population). In 2012, the second national census of child development was completed, and the results were released in April 2013. The second round of data collection involved 289,973 children (96.5 per cent of all children enrolled to begin school in 2012) and provided the first opportunity to explore change in the level of developmental vulnerability for children living in different communities, states and territories within Australia. The AEDI National Report 2012 shows that there has been a significant drop in the level of developmental vulnerability in Australian children from 23.6% in 2009 to 22.0% in 2012.

In 2011, the Australian Government Department of Education, Employment and Workplace Relations (DEEWR) awarded $1.5 million in funding directly to TICHR to explore the 2009 and 2012 AEDI data and deliver on policy focused research. The research focuses on a range of questions pertinent to early childhood development such as:

- Are there jurisdictional differences in the level of developmental vulnerability across Australia?
- Is there a differential impact of living in mining towns vs. non-mining towns for Aboriginal child development?
- How does the AEDI predict later academic outcomes during the primary school years?
- What is the best methodology to use to determine whether communities, LGAs etc have experienced significant change in the childhood development from 2009 to 2012, and what is the best way to communicate this information to various stakeholders?
- How well do perinatal factors (e.g. low birth weight) predict childhood development at 5 years old?

Funder of the Project: Commonwealth of Australia, Department of Education, Canberra.

Acknowledgement: The Australian Government and State and Territory Governments are working in partnership with The Royal Children's Hospital Centre for Community Child Health in Melbourne, the Murdoch Children's Research Institute, and the Telethon Kids Institute, Perth, to deliver the AEDI. The Social Research Centre, Melbourne, is managing the AEDI data.

RANDOMISED CLUSTER CONTROL TRIAL EVALUATING THE IMPACT OF AN EARLY CHILDHOOD EDUCATION AND DEVELOPMENT INITIATIVE ACROSS INDONESIA

Sally Brinkman, Angela Kinnell, Menno Pradhan, Amanda Beatty, Amelia Maika and Elan Satriawan

With a greater scale for improvement in school readiness outcomes, the evaluation of early childhood education and development (ECED) programs in developing countries affords a greater scope for investigation into the facilitators and barriers for success. This ECED program that we are evaluating represents a significant investment on behalf of the Republic of Indonesia and the World Bank.

It is estimated that up to half of Indonesia's population are vulnerable to poverty with the inequality between rich and poor vast. A large disparity in socio-economics, nutrition, education and health exist between districts, with infant and child mortality rates significantly higher in the poorer communities. In addition, children from the poorer villages start school later, complete fewer years of schooling and have higher drop out and repetition rates.

The objective of the ECED Project is to improve poor children's overall development and readiness for further education by (i) increasing the delivery of ECED services in targeted poor communities using a community-driven approach and (ii) developing a sustainable system for delivering ECED services. The project will reach approximately 738,000 children aged 0 to 6 and their parents/caregivers living in about 6,000 poor communities (dusuns) located in 3,000 villages within 50 districts.

The outcomes of the research will enable us: to determine (if and to) what extent the ECED Project improved children's development, attendance and readiness for school; to what extent the ECED Project improved parental awareness and practices; if the Project increased the availability and utilisation of ECED services and if so, how those impacts differed by gender, wealth, and level of service delivery at baseline. By including local academics in the research we will facilitate cultural relevance, local knowledge and contextual relevance to the research (instrument development, fieldwork nuances through to identification of key stakeholders etc). A well designed and implemented impact evaluation will provide a unique opportunity to inform the current and future practices in Indonesia and abroad. In addition the evaluation will utilize outcome instrumentation that can be internationally referenced and thus rigorous piloting and cultural adaptation of internationally recognized instruments will be required.

The AusAID ADRA Grant has enabled the employment of two early career academics based at the University of Gadjah Mada (UGM) in Indonesia. As both academics are teaching university students, building their capacity, skills and knowledge will not only benefit themselves but their current and future students. Building local capacity will decrease the current reliance on "fly-in consultants" from Western countries.

Funder of the Project: Australian Development Research Award (ADRA) awarded by AusAID

EVALUATION OF SOUTH AUSTRALIAN CHILDREN'S CENTRES

Sally Brinkman, Yasmin Harman-Smith

To reduce the impact of social inequality on children's outcomes, the South Australian Government has established a number of Children's Centres across South Australia. By the end of 2013, the Department for Education and Child Development will have established 34 Children's Centres. There will also be four Aboriginal Children's and Family Centres developed as a partnership between the State and Australian Governments. Children's Centres have been located in areas of high need to enable the provision of high quality services to children and families who may not otherwise have access to these supports. Children's Centres are based on a model of integrated practice, bringing together education, health, care, community development activities, and family support services in order to best meet the needs of vulnerable children and families.

Specifically, Children's Centres are tasked to provide universal services with targeted support in order to effect population outcomes in four areas: 1) Children have optimal health, development and learning; 2) Parents provide strong foundations for their children's healthy development and wellbeing; 3) Communities are child and family friendly; 4) Aboriginal children are safe, healthy, culturally strong and confident (Department for Education and Child Development, 2011).

The Telethon Kids Institute through the Fraser Mustard Centre has been engaged to undertake a three year evaluation of these South Australian Children's Centres. The overall aims of the evaluation are to measure process and impact of integrated services in Children's Centres. The overall evaluation approach employs a mixed-method research design, employing qualitative and quantitative measures.

Funder of the Project: Government of South Australia, Department for Education and Child Development

PROOF OF CONCEPT 3

Sally Brinkman, Steve Zubrick, Sven Silburn, Vaughan Carr, John Lynch

Project Support: Veronica Smyth

The Proof of Concept 3 was commissioned by the Population Health Research Network (PHRN) as one of four Proof of Concept Collaborations designed to assess the ability of the PHRN data linkage infrastructure to perform cross-jurisdictional linkage of data. The PoC3 aims to link the Australian Early Development Index (AEDI) together with perinatal and local educational data collections from all jurisdictions. The overall objective is to explore the relationship between perinatal factors and developmental and educational outcomes in early school-aged children.

This longitudinal cohort study uses data linkage methodology to produce timely and cost-effective whole-of-population research outcomes for a defined population. The study design relies entirely on the manipulation and analysis of existing data that was not originally obtained for research purposes, and which is not readily obtainable in other ways. The linked datasets in this project will enable cross-jurisdictional, population wide analyses not previously possible to systematically investigate experiences and conditions that contribute to children's cognitive, social, behavioural and school achievement at the population level – research which can inform government policy and interventions to improve child outcomes at a national level.

The study leverages off existing state based linkage projects in South Australia, Northern Territory, and New South Wales. The investigators undertaking each of these state based linkage projects have come together for the purposes of this national collaboration.

The Proof of Concept 3 aims to link health, early development and education population-based data collections across all Australian states and territories. This national data linkage will be the first step in gaining a better understanding of the relationship between perinatal outcomes and developmental outcomes as measured by the Australian Early Development Index (AEDI) through to educational outcomes.

Funder of the Project: Population Health Research Network

INVESTIGATING THE HOME LANGUAGE ENVIRONMENT IN THE EARLY YEARS

Sally Brinkman, Cate Taylor, Veronica Smyth

Language enables literacy, education, and employment and is one of the major pathways that support human capability formation. Variation in parental talkativeness has shown to be a plausible mechanism for social inequalities in children's language acquisition. This study will use new technology to unobtrusively measure both the language spoken to and the language spoken by the child in the home environment.

The main objective of the study will be to test and trial the practicality of using Language Environment Analysis (LENA) technology for potential future large-scale use in suburban areas of Adelaide. The study will trial LENA in homes with children of varying age. The feasibility of using LENA across age ranges will be examined in this trial by obtaining 16 hour audio recordings, with two direct measures of parent-child language interaction (adult word count, conversational turns) and one measure of language production (child vocalisations). Transcription of audio segments of interest, as well as parental feedback will allow for qualitative analysis. This study will create the necessary platform for further large-scale study that may help reveal the mechanisms behind the social disadvantage in language acquisition for children in Australia.

This is a study conducted by researchers from the Fraser Mustard Centre, a collaboration between the Telethon Kids Institute and the South Australian Department for Education and Child Development. This study will use new technology to unobtrusively measure both the language spoken to and the language spoken by the child in the home environment. The study aims to investigate factors that affect the language environment in the early years of life. The study also aims to examine the feasibility of home observation using Language Environment Analysis (LENA) for infants and young children. This study will provide evidence for potential large-scale study that may help to reveal the mechanisms in language acquisition for children in Australia.

Funder of the Project: Government of South Australia, Department for Education and Child Development

FRASER MUSTARD CENTRE PHD TOP-UP SCHOLARSHIP

Supervisor: Tess Gregory

In honour of Dr Fraser Mustard, the Fraser Mustard PhD Scholarship was established to fund one PhD student, based in the Fraser Mustard Centre, Adelaide. The scholarship provides additional funding support to a PhD candidate who has been awarded an Australian Postgraduate Award (APA) to undertake a PhD. The intent of this is to attract outstanding

students who are passionate about improving developmental, health and educational outcomes for children and young people. It is envisaged that with the appropriate support, these researchers will later contribute to the advancement of policy and practice in the area of child development.

The first Fraser Mustard Centre Top-Up Scholarship was awarded in 2013 to Ms. Shiau Chong. Shiau is completing a PhD in the School of Population Health at the University of Adelaide. Her project is titled: The influence of early childhood temperament and parenting on cognitive, social and health outcomes.

Funder of the Project: Government of South Australia, Department for Education and Child Development

ASSESSING THE DEVELOPMENT, WELL-BEING AND COMMUNITY CONNECTEDNESS OF CHILDREN IN THE MIDDLE YEARS: THE MIDDLE DEVELOPMENT INSTRUMENT FOR AUSTRALIA

Sally Brinkman, Tess Gregory

The Middle Years Development Instrument (MDI) is a validated population-level measure of well-being and contextual assets in middle childhood. The MDI was designed in Canada, to provide schools and communities with pragmatic data to inform policies and practice. This study aims to adapt and psychometrically validate the MDI for use in Australia, including culturally adapting the tool for Australian Aboriginal children. There is a need to move toward ecological solutions rather than band-aid solutions, which attempt to stop problem behaviour without addressing the underlying causal conditions. The MDI will support the incorporation of evidence-based social and emotional learning programming into standard educational practice.

The MDI project is a collaboration between researchers from the Telethon Kids Institute/ University of Western Australia (Sally Brinkman, Tess Gregory, Glenn Pearson), Menzies School of Health Research (Sven Silburn) and the University of British Columbia (Kimberly Schonert-Reichl, Martin Guhn, Anne Gadermann), and policy makers from the Department for Education and Child Development in South Australia (David Engelhardt) and the Department of Education in Western Australia (Rosemary Cahill).

The Middle Development Instrument gives children a voice, an opportunity to communicate to adults about what their experiences are inside and outside of school. The MDI has great potential to provide educators, parents, researchers, and policy makers with much needed information about the psychological and social worlds of children. This project aims to collect MDI data from 7,000 Grade 6 children across South Australia and Western Australia and provide summary information back to policy makers, schools and communities about the health and wellbeing of their children.

Funders of the Project: Australian Research Council Linkage Grant, Government of South Australia, Department for Education and Child Development

FAMILIES SA REUNIFICATION INITIATIVE EVALUATION

Sally Brinkman, Angela Kinnell

This evaluation project proposes to assess process and impact of the South Australian reunification program from 2011 to 2013 and beyond. The staggered implementation of changes to the reunification program from 2011-2013 provide an opportunity to assess the relationship between the nature of service provision, parent experience and child outcomes. Additionally, this evaluation will provide a framework for ongoing assessment of process, parent experience, and the impact on children's outcomes as the reunification program changes in 2013.

In conjunction with Families SA, the Fraser Mustard Centre will develop an Evaluation Framework and plan, including a mixed method approach with quantitative and qualitative research methodologies for evaluation implementation.

The key evaluation questions will include:

- Are there discernible differences in outcomes for children and families who receive a reunification service from offices involved in the 2011 reunification initiative or other reunification services in comparison to outcomes for other children and families?
- What factors have contributed to these differences?

Funder of the Project: Government of South Australia, Department for Education and Child Development

STRONG START PROGRAM EVALUATION

Sally Brinkman, Yasmin Harman-Smith

Researchers from the Fraser Mustard Centre have been engaged to support the Strong Start program which is designed to deliver home based services to families identified as experiencing significant and complex vulnerabilities. The project recognises that all children have the right to health, wellbeing and safety in a supportive family and community environment. The Strong Start project also recognises that parents have the primary responsibility for raising their children; however some families require more support than others. The pilot program will initially be developed in the northern suburbs of SA and will build on the existing interagency partnerships. The broad aims of the pilot include:

- Engage pregnant women and families in the antenatal period in order to maximize opportunities for effective intervention.
- Improve families' capacity to parent their children through building strength and resilience, and reducing vulnerabilities.
- Improve families' awareness of infants and children's health and development needs.
- Enhance the development and learning capacity of infants and children.
- Improve the health and wellbeing outcomes for infants, children and families.
- Facilitate access to networks of family support services.
- Facilitate services within the network to have a prevention orientation.
- Strengthen the voice of children and families in the community.

Funder of the Project: Government of South Australia, Department for Education and Child Development

AEDI ANALYSES FOR SA AND SUPPORT FOR DEPARTMENT OF EDUCATION AND CHILD DEVELOPMENT POPULATION PLANNING

Sally Brinkman, Tess Gregory

Project Support: Yasmin Harman-Smith

The AEDI is undertaken once every three years by the Department of Education, Canberra as a progress measure of future human capital for the Council of Australian Governments. The AEDI has been completed in 2009 and 2012 across South Australia and the results reveal patterns of child development across the state. Although simple descriptive statistics have been produced and mapped data for communities are available via the national AEDI website – the AEDI results have not been critically analysed for SA.

This project will help to inform the state and in particular the Department of Education and Child Development regarding the AEDI results in SA. Along with the AEDI analyses, resources to help facilitate conversations at the community through to Departmental level will be produced – aimed at supporting the use of population data.

Specifically, this project aims to:

- Determine if the areas where Children's Centres and the Learning Together program is operating are showing a different pattern of AEDI results compared to areas without?
- Determine if there are specific population groups that have improved or not, and if not – why not? Are there other characteristics about these groups where we see poor results?
- Between 2009 and 2013 in SA there was a 6 percentage point drop in the percentage of Aboriginal children who spoke a language other than English in the AEDI. This pattern will be investigated.
- Consultation will be undertaken to identify policy and service changes which may have impacted differently on South Australian children born in 2003/04 compared to those born in 2006/07.

Funder of the Project: Government of South Australia, Department for Education and Child Development

GENDER GAP ANALYSIS – BOYS AND GIRLS IN SOUTH AUSTRALIA

Sally Brinkman, Angela Kinnell, Yasmin Harman-Smith

There is growing international evidence about the gap in educational outcomes between boys and girls. Although this trend appears to be evident in South Australia and national data, to date, little has been undertaken to document this trend and to understand the trajectories of boys as compared with girls, identify the drivers of these developmental pathways and identify potential strategies for intervention. Thus, the project proposes to test whether there is a sufficient policy rationale for government to implement new strategies to respond to this issue and, if so, present options forward.

The results of the 2009 AEDI highlighted large differences between South Australian boys and girls in child development outcomes at school entry. The Department for Education and Child Development commissioned this report to understand how such gender differences in early childhood may influence outcomes later in life. The report includes gender differences in education, health and social circumstances across the life-course. Knowledge of this evidence base is crucial if we are to improve outcomes for all children and young people and reduce inequity.

Funder of the Project: Government of South Australia, Department for Education and Child Development

THRIVING IN ADVERSITY

Sally Brinkman, Tess Gregory

Project Support:Alanna Sincovich

Both NAPLAN and AEDI data reveal that although socioeconomic status is a strong predictor of developmental and educational outcomes - it is not destiny. Despite adversity in some low income communities there are individuals, schools and communities that are performing higher than would be predicted by statistical models. This project seeks to explore the characteristics of these individuals, schools and communities, which thrive in adversity, to determine whether there are lessons to be learnt that may be transferable to other places.

The Thriving in Adversity project will involve qualitative and quantitative analysis to investigate these high performing individuals, schools and communities to better understand what is driving this success. This will involve developing reliable statistically risk adjusted (value added modelling) techniques to identify the genuine high performing statistical outliers, developing qualitative methodologies to identify the tributes that foster resilience.

The project will also link closely with the Seligman consultancy to promote positive messages around taking action to promote resilience and wellbeing at individual, school and community level.

Funder of the Project: Government of South Australia, Department for Education and Child Development

Policy briefs, research snapshots, professional development training, professional associated magazines:

Sally Brinkman and Tess Gregory – AEDI

Research Snapshot: Jurisdictional differences in the wellbeing of 5 year olds. Australian Government, Canberra. Available at: www.aedi.org.au.

Tess Gregory and Sally Brinkman – AEDI Research Snapshot: Comparing results 2009 and 2012. Australian Government, Canberra. Available at: www.aedi.org.au.

Sally Brinkman - Australian Institute of Family Studies. Invited National Webinar Presentation. The Australian Early Development Index (AEDI): Results over time, and the work of the Fraser Mustard Centre. Child Family Community Australia.

Sally Brinkman - Speech Pathology Australia. Professional Development Training for Speech Pathologists. Day long PD entitled: Child language research update: Integrating clinical & public health perspectives.

Sally Brinkman - South Australian Child and Maternal Health Nurses Professional Development Day. Progressive universalism, population data and planning service provision. October.

Sally Brinkman - Productivity Commission. Invited "expert" for the Inquiry into Child Care in Australia.

Media:

Sally Brinkman - Magazine Article. "Australia study links EDI results to government policies" University of Alberta Magazine.

Sally Brinkman - Radio, Live Talk Back "Children's development before school", 6PR, Perth.

Sally Brinkman - Newspaper, Community support for child development". The Border Watch.

Sally Brinkman - Radio, Live Interview. Child

development and community supports in the south east of SA. ABC Mt Gambia.

Sally Brinkman - Television, Launch of the Pacific Early Age Readiness for Learning Partnership and funding between the World Bank and the Government of Indonesia. Chanel 2, Tonga.

Developmental Pathways in WA Children Project

Fiona Stanley (University of Western Australia (UWA), Telethon Institute for Child Health Research (TICHR)); Helen Leonard (UWA, TICHR); Nicholas de Klerk (UWA, TICHR); Jianghong Li (Curtin University of Technology, TICHR); Natasha Nassar (UWA, University of Sydney); Stephen Zubrick (UWA, TICHR); Catherine Taylor (UWA, TICHR); Amanda Langridge (UWA, TICHR); Eddie Bartnik (WA Mental Health Commission); Cheryl Gwilliam (WA Department of the Attorney General); Ian Johnson (WA Department of Corrective Services; Ruth Sheen (WA Department of Training); Tim Marney (WA Department of Treasury and Finance); Karl O'Callaghan (WA Police); Sharyn O'Neill (WA Department of Education); Grahame Searle (WA Department of Housing); Ronald Chalmers (Disability Services Commission WA); Jenni Perkins (WA Department for Communities); Cliff Weeks (WA Department of Indigenous Affairs); Diana Rosman (Department of Health WA); and Bryant Stokes (Department of Health WA)

The Developmental Pathways Project is a landmark project taking a multidisciplinary and holistic approach to investigate the pathways to health and wellbeing, education, disability, child abuse and neglect, and juvenile delinquency outcomes among Western Australian children and youth. To achieve this, researchers from the Telethon Institute for Child Health Research and the University of Western Australia have been working in collaboration with a number of state government departments, including the WA Departments of Health, Education, Training, School Curriculum and Standards Authority, Child Protection and Family Services, Corrective Services, Communities, Aboriginal Affairs, Treasury, Housing, Attorney General, the Disability Services Commission, the Mental Health Commission, and WA Police. The project has established the process of linking together de-identified longitudinal, population-based data collected and stored by a large number of these WA government departments and the Telethon Institute, to create a fantastic cost-effective research and policy planning/evaluation resource. The project has also established a Directors' General Steering Committee who meets twice a year to discuss how to best use these joined up data and joined up agency resource. The project also has a Consumer and Community Reference Group who meet four times a year to provide an oversight role for governance, standards and practices relating to the project from a community perspective.

The linked data are being used by researchers and the respective departments to identify multi-level and early determinants of developmental outcomes and the interrelationships among them. Through the effective communication of the research findings, future government agency policies, practice and planning initiatives will be more preventative, culturally appropriate and cost efficient, and we have encouraged cross-agency collaboration to ensure improved health, well-being and development of children and youth, their families and their communities.

Funders of the project: The Developmental Pathways Project was made possible by the generous cash and in-kind contributions made by all of the collaborating organisations and government departments, which has been matched by the Australian Research Council (ARC) through two consecutive ARC Linkage Project Grants.

The Developmental Pathways Project supports several postgraduate students and postdoctoral fellows, to conduct individual research projects which answer specific research and policy relevant questions within and across the themes and scope of the overall project.

CHILD ABUSE AND NEGLECT

Conducted by Dr Melissa O'Donnell

Dr Melissa O'Donnell is an NHMRC Early Career Fellow and a Psychologist who completed her PhD in 2009 through the University of Western Australia. Her research uses longitudinal population data provided through the Developmental Pathways Project. This administrative data is being used to: investigate emergency department presentations and hospital admissions related to child abuse and neglect; determine the mental health and juvenile justice outcomes of children who have contact with the child protection system; and investigate the child, family and community characteristics which increase or reduce vulnerability to child abuse and neglect.

Conducted by Miriam McLean

Miriam McLean is completing her doctorate on the Developmental Pathways Project. Her project is titled "'Educational outcomes of children in contact with the child protection system: A longitudinal population study'". The aim of this study is to examine the educational outcomes of children in contact with the child protection system. This project is innovative in that it will use linked government administrative data from Child Protection, Health, Education and Disability Services through TICHR's Developmental Pathways Project, to conduct a longitudinal analysis of prospective data from a large cohort of children. Currently, Western Australia is the only Australian state that has a comprehensive data linkage system including children's education and child protection data, along with data on an array of child, parental and community characteristics. Using this linked data will assist in overcoming the many methodological difficulties associated with maltreatment research, and enable a much greater understanding of the relationships between maltreatment and out of home care with educational outcomes, taking into account a range of risk factors at the child, parental and community levels.

ABORIGINAL HEALTH RESEARCH

Conducted by Glenn Pearson

Glenn Pearson, a Noongar from Western Australia, and Manager of Aboriginal Health Research at the Institute, is completing his Doctorate on the Developmental Pathways Project. His qualitative research PhD project explores how the delivery of health, education and child protection services provided by the WA State Government to Aboriginal clients is mediated by the perceptions Non Aboriginal and Aboriginal people hold of themselves and each other in the provision and receipt of these services.

JUVENILE OFFENDING

Conducted by Anna Ferrante

Anna Ferrante is an Associate Professor at the Centre for Data Linkage, Curtin University, formerly a Research Associate Professor at the

Crime Research Centre, University of Western Australia. As part of the Developmental Pathways Project, Anna is undertaking a population-based study of the dimensions and development of delinquency in Western Australian children. The aim of the project is to contribute to a better understanding of the dimensions of juvenile delinquency and of the impact of various factors on the development of delinquency over the life-course. By exploring the interactions between risk factors and their effect on offending, it may be possible to map 'pathways' from early childhood to juvenile delinquency and later criminal behaviour.

Conducted by Jocelyn Jones

Jocelyn Jones is completing her doctorate through the Developmental Pathways Project. Her project is titled 'Exploring the pathways to contact with juvenile justice in Aboriginal and Torres Strait Islander children: developing a profile of the risk and protective factors to support a strategy for change'. Using linked longitudinal population data provided through the DPP this project seeks to develop a profile of the developmental, health, socio-economic, racial and demographic factors associated with risk, protective and resilience factors that contribute to juvenile delinquency in Aboriginal and Torres Strait Islander Children.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Conducted by Dr Desiree Silva

Dr Desiree Silva is a paediatrician, and Professor of Paediatric Medicine at Joondalup Health Campus and UWA. Due to the escalation of mental health issues in children, Desiree commenced a PhD through UWA and the Telethon Institute for Child Health Research on the risk factors and outcomes of children and adolescents diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) in Western Australia. Her PhD project uses longitudinal population data provided through the Developmental Pathways Project. This administrative data, along with questionnaire data, is being used to: identify potential antenatal and early neonatal risk factors associated with children requiring treatment with stimulant medication; explore hospital and emergency morbidity, accident related hospitalisation risk, criminal and antisocial behaviour, and service needs associated with children on stimulant treatment for ADHD; examine education outcomes of children diagnosed with ADHD and their level of stimulant medication treatment; and explore the mental health burden of parents and family functioning of children diagnosed and treated with pharmacotherapy for ADHD in WA.

MENTAL HEALTH

Conducted by Janice Wong

Janice Wong is completing her doctorate on the Developmental Pathways Project. Her project is titled 'The relationship between educational and mental health outcomes for Western Australian children: A longitudinal population study". Using linked longitudinal population data provided through the DPP, this subproject seeks to explore the dynamic relationship between children's educational outcomes and their mental health, whilst taking into account variables that have been shown to impact on this relationship. Children who are vulnerable to mental health problems are subsequently at risk of experiencing interference with development, and more specifically, with schooling, and the development of their identity. Results of this study will potentially inform the development of suitable interventions, ultimately with the aim to decrease the prevalence of mental health issues and improve educational outcomes.

Conducted by Nan Hu

Nan Hu is completing his doctorate on the Developmental Pathways Project. His project is titled "An investigation of the developmental pathways to hospitalized deliberate self-harm behaviours (DSH) among young people: a birth cohort study using cross jurisdictional linked data in Western Australia (WA)". This project has two main aims: 1) To examine the epidemiological characteristics and the current trend of deliberate self-harm related hospitalizations in young people of 10-30 years old in Western Australia. 2) To investigate how specific biological, psychological and social factors at the child, family, school and community levels interact to influence the developmental pathways to deliberate self-harm related hospitalization among young people. This aim will be achieved by undertaking five sub-studies respectively focusing on birth factors, family and community factors, child maltreatment, educational outcome, psychiatric correlates, and certain types of intellectual and developmental disabilities.

EARLY CHILD DEVELOPMENT AND EDUCATION

Conducted by Megan Bell

Megan Bell is completing her combined Masters and PhD through the Developmental Pathways Project and the University of Western Australia. Megan's project, How do individual, family and neighbourhood characteristics influence children's early development and academic achievement? A linked data population study, aims to examine how early childhood development is related to educational achievement. Using a linked data approach, we will combine children's health, demographic and achievement information with data on their parents, and the neighbourhoods they live in. This method of investigation will allow us to examine how child, parent and neighbourhood characteristics can positively or negatively influence development up to school entry. Children's outcomes will be measured using the Australian Early Development Index (AEDI), which is a nation-wide assessment which gives an indication of child development at age 5. We will also examine whether children's scores on the AEDI are related to their achievement on the National Assessment Program - Literacy and Numeracy (NAPLAN) at age 8. This analysis will provide information on how developmental level at school entry is associated with achievement levels in later school. This study will identify the population subgroups at highest risk of developmental and educational disadvantage in Western Australia, which will enable the development of interventions targeting the most vulnerable groups.

The Developmental Pathways Project also facilitates the provision of de-identified non-health linked population level data to a number of other research projects conducted within other research institutions and WA Government, including those led by Prof Jablensky (Pathways of Risk from Conception to Disease: A Population-Based Study of the Offspring of Women with Bipolar Disorder and Schizophrenia); Assoc Prof Tony Butler (Does Traumatic Brain Injury (TBI) lead to offending behaviour?); and Dr Colleen O'Leary (Investigating the effect of a maternal alcohol-related diagnosis on the educational, juvenile

justice, and child protection outcomes of their children and Examining the effect of the dose, pattern, and timing of prenatal alcohol exposure on educational outcomes). We are assisting the WA Mental Health Commission in an evaluation of Supported Accommodation Services for people with severe and persistent mental health problems, to try to ascertain if supported accommodation results in improved health and mental health for residents. We are also working with Ngala to investigate where their services are being most utilised.

In 2013 we were involved in the WA Crime Prevention initiative and provided information and presentations to the WA Crime Prevention Council on hotspots for Juvenile crime, and areas in the WA metropolitan area which are in need of extra support and services for families and children.

Environmental determinants of health

This topic was focussed on the environmental determinants of health, with a focus on the built environment and ambient air pollution exposures. The following studies led by the investigator were published since the last report.

ACCESS TO ALCOHOL OUTLETS, ALCOHOL CONSUMPTION AND MENTAL HEALTH

Gavin Pereira, Lisa Wood, Sarah Foster, Fatima Haggar Pereira, Gavin, et al.

"Access to alcohol outlets, alcohol consumption and mental health." PloS one 8.1 (2013): e53461.

The objective of this study was to investigate residential exposure to alcohol outlets in relation to alcohol consumption and mental health morbidity (anxiety, stress, and depression). This was a cross-sectional study of 6,837 adults obtained from a population representative sample for the period 2006–2009 in Perth, Western Australia. The number of alcohol outlets was ascertained for a neighbourhood around the residential address. We assessed associations between total alcohol consumption, harmful alcohol consumption (7–10 drinks containing 10 g of alcohol for men, 5–6 drinks for women) and medically diagnosed and hospital contacts (for anxiety, stress, and depression). Harmful consumption of alcohol per month and the number of standard drinks of alcohol consumed per drinking day was associated with the prevalence of alcohol outlets in the neighbourhood. Risk of hospital contact for anxiety, stress, or depression was 50% greater for those with a liquor store in the neighbourhood compared to those without. These associations were independent of socioeconomic risk factors. This study was cited in the Review of the Liquor Control Act of 1988 and a submission by the Cancer Council of WA for the Review of the Act.

THE ASSOCIATION BETWEEN NEIGHBORHOOD GREENNESS AND WEIGHT STATUS

Gavin Pereira, Hayley Christian, Sarah Foster, Bryan J Boruff, Fiona Bull, Matthew Knuiman, Billie Giles-Corti Pereira, Gavin, et al.

"The association between neighborhood greenness and weight status: an observational study in Perth Western Australia." Environmental Health 12.1 (2013): 49.

This study was an investigation of weight status and neighborhood greenness using objectively measured satellite remote sensing for a large population representative sample of 10,208 young adults (16–24 years), mid-age adults (25–64 years) and older adults (65+ years) for the period 2004–2009 in Perth, Western Australia. Neighborhood greenness was ascertained for a neighbourhood around each participant's address using the Normalized Difference Vegetation Index (NDVI) obtained from high-resolution imagery from the LandSat satellite. After accounting for socioeconomic and other risk factors, participants in the greenest areas were as much as 22% less likely to be obese and 16% less likely to be overweight. Research examining neighborhood characteristics correlated with variability in greenness will help better understand these relationships.

FINE PARTICULATE MATTER AND RISK OF PRETERM BIRTH IN CONNECTICUT

Gavin Pereira, Kathleen Belanger, Keita Ebisu and Michelle L. Bell Pereira, Gavin, et al.

"Fine Particulate Matter and Risk of Preterm Birth in Connecticut in 2000–2006: A Longitudinal Study." American journal of epidemiology 179.1 (2014): 67-74.

Several studies have examined associations between fine atmospheric particulates and preterm birth, but it is uncertain whether results were affected by individual predispositions (e.g., genetic factors, social conditions) that might vary considerably between women. We tested the hypothesis that a woman is at greater risk of preterm delivery when she has had elevated exposure to particulates during a pregnancy than when she has not by comparing pregnancies in the same woman. From 271,204 births, we selected 29,175 women who had vaginal singleton live births at least twice in Connecticut in 2000–2006. Analyses matched pregnancies to the same woman. Pregnancies with elevated particulate exposure were more likely to result in preterm birth than were other pregnancies to the same woman at lower exposure. Associations were most pronounced in the first trimester and among Hispanic women.

RESEARCH SUPPORT

Gavin Pereira was supported by an NHMRC Early Career Fellowship (1052236). NHMRC Program Grant (572742). Western Australian Health Promotion Foundation grant (18922)

Human Capability

GETTING OUR STORY RIGHT

David Lawrence, Francis Mitrou, Daniel Christensen, Glenn Pearson, with Geoff Davis (Western Australian Department of Health), and Sybille McKeown and Brent Bufton (Australian Bureau of Statistics)

The Getting Our Story Right project is a collaboration between the Telethon Kids Institute, the Australian Bureau of Statistics (ABS) and the Western Australian Department of Health and aims to explore and develop different methods for deriving Indigenous status from multiple data sources using the WA Data Linkage System and examine the impact of these methods on a sample of health and educational outcomes among the Indigenous population.

Various methods of deriving consistent Indigenous status from a linked data source will be explored and the impact of these methods examined against a selection of health and educational outcomes such as mortality rates, hospitalisation rates, and school-based reading and writing scores from standardised tests.

The overall aim of the project is to produce a set of recommendations for agencies and researchers responsible for the provision of Aboriginal and Torres Strait Islander Statistics, particularly with reference to COAG 'Closing the Gap' indicators. It is envisaged that these recommendations will help agencies and researchers produce consistent, reproducible and meaningful statistics in order to assess the health and wellbeing of Aboriginal people.

Funders of the project: COAG, ARC Discovery Grant DP0877513.

SUGAR SWEETENED BEVERAGE CONSUMPTION BY AUSTRALIAN CHILDREN: IMPLICATIONS FOR PUBLIC HEALTH STRATEGY

Katherine Hafekost, Francis Mitrou, David Lawrence and Stephen R. Zubrick

Consumption of sugar sweetened beverages (SSB) has been linked to unhealthy weight gain and nutrition related chronic disease. Despite public health efforts to reduce consumption, such as limiting sales of these products in schools and restrictions on marketing, Australian children's intake remains high. In addition, little up-to-date information about the primary purchase source of SSB, consumption patterns and the dietary and demographic profile of SSB consumption in children was available. We used data from the 2007 Australian National Children's Nutrition and Physical Activity to address these issues.

We found that SSB consumption was high and patterns of consumption varied by age. The primary source of SSB was from supermarkets with less than 17 per cent of products being sourced from fast-food establishments and school canteens. Further, the majority of SSBs were consumed at home. We found children whose parents had lower levels of education consumed more SSB on average, while children whose parents had higher education levels were more likely to favour sweetened juices and flavoured milks.

This research highlights the need for public health interventions which are evidence based and target the primary source of SSBs in order to reduce current levels of intake by Australian children. Additionally, education of parents and children regarding the health consequences of high consumption of both carbonated and non-carbonated SSBs is required.

Funders of the project: NHMRC program grant #572742.

HOW MULTIPLE GENERATIONS OF MENTAL HEALTH PROBLEMS IN FAMILIES INFLUENCES THE WELLBEING OF CHILDREN

Kirsten Hancock, Francis Mitrou, David Lawrence and Stephen R. Zubrick, with Megan Shipley (Australian Government Department of Social Services)

Research has consistently shown that children of parents with mental health problems are at greater risk of also developing mental health problems. Yet there is limited research around how these mental health relationships evolve over multiple generations, beyond the initial parent-child relationship. In this study, we used data collected from 4,600 families participating in Growing Up in Australia: The Longitudinal Study of Australian Children to examine the mental health relationships across three generations of Australian families. Our results show that the mental health of grandparents matters for children, even in the absence of problems in the parent generation. In our next phase of work we are examining how multiple generations of mental health problems impact upon specific mental health problems for children, such as conduct problems or emotional problems, and how these differ according to mental health on the maternal and paternal side of families.

Funders of the project: NHMRC program grant #572742.

THE INFLUENCE OF LONG-TERM JOBLESSNESS AND SEPARATION OF GRANDPARENTS ON GRANDCHILDREN

Kirsten Hancock and Stephen R. Zubrick, with Ben Edwards (Australian Institute of Family Studies)

We have understood for many years that family experiences such as separation and/or joblessness have close intergenerational links. To date, there have been limited opportunities to examine how these intergenerational relationships work across three generations of family members. In collaboration with the Australian Institute of Family Studies, this project uses data from over 8,000 families participating in Growing Up in Australia and examines the extent to which joblessness and family separation transfers across generations, and how a continuing family history of these disadvantages relates to a variety of outcomes for children, including their social and emotional wellbeing and performance at school. The initial findings from the project were published in the Longitudinal Study of Australian Children 2012 Annual Statistical Report, with further work currently underway.

Funders of the project: NHMRC program grant #572742.

STUDENT ATTENDANCE AND EDUCATIONAL OUTCOMES OF WESTERN AUSTRALIAN STUDENTS

Kirsten Hancock, Carrington Shepherd, David Lawrence and Stephen R. Zubrick, with the Western Australian Department of Education

For this project we used WA Department of Education enrolment, attendance and NAPLAN achievement data from 2008 to 2012 to assess the attendance patterns of around 400,000 primary and secondary students across the 5-year period, and how these patterns vary for students with different characteristics. We examined the extent to which authorised and unauthorised absences from school are related to NAPLAN achievement after controlling for a range of factors, how absence rates in previous years relate to current achievement levels, whether there is a "safe" threshold of absence for students, and whether students who improve their attendance at school improve their NAPLAN scores. The results of the study have important implications for students, parents and educators, and were made available in August 2013.

Funders of the project: Australian Government Department of Education, Employment and Workplace Relations.

ATTITUDE, ATTENDANCE AND ACHIEVEMENT: A LONGITUDINAL VIEW OF STUDENT DEVELOPMENT AND PARTICIPATION IN EDUCATION OVER TIME.

Kirsten Hancock, David Lawrence, Cate Taylor and Stephen R. Zubrick

This project is an extension of our earlier work, and will examine the complex interplay between students' attitudes and behavior, patterns of absence and academic achievement. The first

part of the study will examine whether school absence in the early years is a precursor for poor attitude and behavior in later years, and if so, how early do problems emerge? The second part of the study will examine the fine level detail that accompanies each episode of absence, addressing questions of whether short, frequent absences are more disruptive for students that long, infrequent absences, and if absences that occur earlier in the semester are more disruptive than those which occur later in the semester. The reasons provided for these absences are also of interest, and whether absences that occur for family or social reasons have different impacts to absences that are due to illness. Using the WA Department of Education database of over 400,000 students, including longitudinal measures of attitude and behavior, attendance and achievement, this project will address significant knowledge gaps and provide education policy makers with useful information relevant to Australian students in the Australian context.

Funders of the project: NHMRC program grant #572742.

HIGHLY PROTECTIVE PARENTING AND CHILD BMI

Kirsten Hancock, David Lawrence and Stephen R. Zubrick

In recent decades rates of child overweight and obesity have increased, while children have become less active and more sedentary. Over the same period, parents have become increasingly concerned for children's safety and independent mobility, even though the risks of harmful events have not changed. Though some have argued that a trend towards overprotective parenting, and subsequent restrictions on children's independent mobility, may be linked to the increase in rates of child overweight and obesity, there is very limited research available to support these claims. The aim of this study is to establish if any association can be drawn between child obesity and maternal protectiveness. Our initial findings suggest that maternal overprotection is more common amongst disadvantaged families, and that as children become older, those with highly protective mothers are more likely to be overweight or obese than other children. The results provide evidence of a link between maternal protectiveness and child BMI, however further research is required to understand the mechanisms that underpin this link.

Funders of the project: NHMRC program grant #572742

YOUNG MINDS MATTER: THE SECOND AUSTRALIAN CHILD AND ADOLESCENT SURVEY OF MENTAL HEALTH AND WELLBEING

Katrina Boterhoven de Haan, Sarah Johnson, Jennifer Hafekost, David Lawrence, Stephen R. Zubrick, with Michael Sawyer (University of Adelaide) and John Ainley (Australian Council for Educational Research)

The National Survey of Mental Health and Wellbeing includes three main components - a population-based survey of adults, a service-based survey of people with low-prevalence psychotic disorders, and a population survey of children. The first Child and Adolescent component was conducted in 1998. The Telethon Kids Institute is currently conducting Young Minds Matter, the second child and adolescent component of the National Survey of Mental health and Wellbeing, in collaboration with Roy Morgan Research. Following pilot testing and a dress rehearsal main fieldwork for the survey commenced on 31 May 2013 and is due to be completed April 2014. A final publication of survey results is due for release in November 2014.

The broad aims of the National Survey of Mental Health and Wellbeing initiative are to determine how many Australians have which mental disorders, what is the impact of these disorders (on individuals, families and communities), what services are being used by people with mental disorders, and what services are needed for people with mental disorders and their families.

Funders of the project: Australian Government Department of Health.

EARLY LIFE INFLUENCES ON CHILD AND ADOLESCENT MENTAL HEALTH PROBLEMS: A LIFE-COURSE APPROACH TO PREVENTION AND INTERVENTION

Investigators: Dr Monique Robinson (Supervisor: W/Professor Stephen R. Zubrick)

It has been suggested that the best method for avoiding poor mental health outcomes is to build and promote positive outcomes right from the very start of life. The goal then shifts from treating problems after they have occurred, to a model enabling the formation and promotion of positive mental health outcomes. However, we have predominantly used early childhood as the start point for development. This project exists within this new paradigm, exploring the early life influences on behavioural development.

Funders of the project: Australian Rotary Health Colin Dodds Postdoctoral Research Fellowship (2011-2013) and NHMRC Early Career Fellowship (2013-2016).

PARENT-CHILD BOOK READING ACROSS EARLY CHILDHOOD AND CHILD VOCABULARY IN THE EARLY SCHOOL YEARS: FINDINGS FROM THE LONGITUDINAL STUDY OF AUSTRALIAN CHILDREN

Brad Farrant, Stephen R. Zubrick

Vocabulary knowledge is a critical component of school readiness. The current study investigated the extent to which low levels of joint attention in infancy and parent-child book reading across early childhood increased the risk of children having poor vocabulary around the time of school entry (using data from the Longitudinal Study of Australian Children). As hypothesised, children who had low levels of joint attention at wave 1 were significantly more likely to have poor receptive vocabulary at wave 3. Furthermore, children who had low levels of parent-child book reading across early childhood were two and a half times more likely to have poor vocabulary at wave 3. These results converge with the findings of training studies and underline the importance of educating current and future parents about the pivotal roles of joint attention and parent-child book reading for children's language development and hence their readiness for school.

Funders of the project: NHMRC Program Grant #572742.

LEARNING BETTER TOGETHER: CONNECTING THE STRENGTHS OF ABORIGINAL PEOPLE AND CULTURE TO ENHANCE EARLY CHILDHOOD DEVELOPMENT

Brad Farrant, Stephen R. Zubrick, Glenn Pearson

Aboriginal children are twice as likely to be classified as developmentally vulnerable when they start school. Aboriginal people are actively seeking involvement in the design of policies and

services to improve outcomes for their children. They want them to reflect more of their values and circumstances because this will improve their relevance and uptake. This project will consult and collaborate with Aboriginal parents, families and elders to guide research (using three large existing datasets) into the factors that prompt, facilitate and constrain the early childhood development of Aboriginal children and to direct the translation of the findings into a suite of culturally appropriate and empowering policies and practices.

Funders of the project: NHMRC Program Grant #572742.

LANGUAGE STABILITY AND CHANGE

Cate Taylor, Daniel Christensen, David Lawrence, Francis Mitrou, Stephen R. Zubrick.

Receptive vocabulary develops rapidly in early childhood and builds the foundation for language acquisition and literacy. Variation in receptive vocabulary ability is associated with variation in children's school achievement, and low receptive vocabulary ability is a risk factor for under-achievement at school. This study looks a facilitators, prompts and constraints of receptive vocabulary development, as well as asking what normal development looks like.

A range of analytic techniques have been used in this study. Multivariate growth curve modelling was used to estimate trajectories of receptive vocabulary development in relation to a wide range of candidate child, maternal and family level influences on receptive vocabulary development from 4-8 years. Logistic regression has been used to assess risks, and to quantify how well early receptive vocabulary predicts subsequent performance.

Risks for receptive vocabulary delay at 4 years, in order of magnitude, were: Maternal Non-English Speaking Background (NESB), low school readiness, child not read to at home, four or more siblings, low family income, low birthweight, low maternal education, maternal mental health distress, low maternal parenting consistency, and high child temperament reactivity. None of these risks were associated with a lower rate of growth from 4-8 years. Instead, maternal NESB, low school readiness and maternal mental health distress were associated with a higher rate of growth, although not sufficient to close the receptive vocabulary gap for children with and without these risks at 8 years. SES area disadvantage was not a risk for low receptive vocabulary ability at 4 years but was the only risk associated with a lower rate of growth in receptive vocabulary ability. At 8 years, the gap between children with and without SES area disadvantage was equivalent to eight months of receptive vocabulary growth. These results are consistent with other studies that have shown that social gradients in children's developmental outcomes increase over time.

Future work will look at the consequences of receptive vocabulary development for academic performance, as well as further assess the implications of our findings for policy and interventions.

Funders of the project: NHMRC Program Grant #572742.

TWINS AND SINGLETONS WITH SPECIFIC LANGUAGE IMPAIRMENT

Catherine Taylor, Stephen Zubrick with Mabel Rice, Shelley Smith, Javier Gayan, and Hugh Catts

The over-arching objective of this program of investigation is to identify the pathogenesis and ontogeny of Specific Language Impairment (SLI). The specific aims for this cycle of funding are: 1) Document longitudinal language acquisition of twins ages 2-14 years, and compare to singletons at 2, 6, 9, and 14 years; 2) Identify twinning effects on early language acquisition and describe the longitudinal course of such effects; 3) Develop multivariate models of biological and environmental risk for twinning effects and for SLI, and compare for possible overlapping etiology. and 4) Evaluate models of age-graded genetic effects via converging methods. In this past year we have documented an increased likelihood of late language emergence in twin toddlers compared to singleborn children and that this is modulated by zygosity and gender differences. Heritability estimates are consistent with previous research for vocabulary and add further suggestion of heritable differences in early grammar acquisition.

Funders of the project: National Institutes of Health (RO1DC05226, P30DC005803, P30HD002528).

FUTURE UNDER THREAT: CLIMATE CHANGE AND CHILDREN'S HEALTH

Brad Farrant, with Fiona Armstrong (Climate and Health Alliance, Victoria) and Glenn Albrecht (Murdoch University)

Climate change has been widely recognised by leading public health organisations and prestigious peer reviewed journals as the biggest global health threat of the 21st century. Along with the old and disadvantaged, children are particularly vulnerable to the negative effects of climate change. Children suffer around 90% of the disease burden from climate change. Even if current international carbon reduction commitments are honoured, the global temperature rise is predicted to be more than double the internationally agreed target of 2°C. Humanity continues to pour record amounts of CO2 into the atmosphere. It has been estimated that climate change will mean that Australian children will face a 30% to 100% increase across selected health risks by 2050. Indeed, if we fail to act, future generations of Australians may face a three- to 15-fold increase in these health risks by 2100. We are only beginning to understand the impacts that climate change will have on children's physical and mental health. More research at the regional and local levels is desperately needed so we can adequately understand, prepare for and adapt to the impacts of climate change. The existence of cost effective ways to reduce climate change means there is no excuse for inaction. Climate change and the carbon-intensive energy system are currently costing 1.7% of global GDP and are expected to reach 3.5% by 2030. This is much higher than the cost of shifting to a low carbon economy. Right now the science is telling us that we are not doing enough. As children are innocent and non-consenting victims of climate change, adults have an ethical obligation to do everything possible to prevent further damage to their ability to thrive in the future. To do otherwise is to ignore the very thing many of us see as the most important reason for living.

HUMAN DEVELOPMENT OF INDIGENOUS VERSUS NON-INDIGENOUS POPULATIONS IN DEVELOPED NATIONS

Francis Mitrou, David Lawrence and Stephen R. Zubrick, with Martin Cooke (University of Waterloo, Canada), Eric Guimond (Department of Aboriginal Affairs and Northern Development, Canada), and David Povah and Elena Mobilia (Australian Bureau of Statistics)

Understanding the economics of Indigenous disadvantage is of particular importance if we are to lift Aboriginal children and families out

of poverty and reduce over-representation in human services agencies in the foreseeable future. We have a long-standing collaboration between The University of Waterloo (Canada), the Department of Aboriginal Affairs and Northern Development Canada, and the Australian Bureau of Statistics, to examine indicators of human development among Aboriginal populations in colonised Western nations. This includes plans for several papers over the next 2 years, the first of which uses a representative cohorts methodology to investigate changes in key socio-economic outcomes of Indigenous and non-Indigenous persons in three developed nations (Australia, Canada, and New Zealand) from 1981–2006.

Funders of the project: NHMRC program grant #572742.

TRENDS IN SUGAR SUPPLY AND CONSUMPTION IN AUSTRALIA: IS THERE AN AUSTRALIAN PARADOX?

Wayne Rikkers, David Lawrence, Katherine Hafekost, Francis Mitrou, and Stephen R. Zubrick

High consumption of refined carbohydrate, in particular sugar, has been identified as a possible contributory factor in greater risk of excess weight gain. In spite of data limitations, some researchers have suggested that Australian sugar consumption has decreased over the same time period that obesity has increased, labelling this a so called 'Australian Paradox'.

To examine this anomaly further, we attempted to estimate the Australian sugar supply and consumption for the time period 1988 to 2010, but found we could not produce a reliable and robust estimate of total sugars in the Australian diet due to data limitations and a lack of current data sources. However, available import data showed large increases in the volume and value of imported sweetened and processed food products over that same period. Our research determined that the Australian Paradox researchers used data which did not include the sugar contained in these imported products. Therefore we concluded that the Australian Paradox assertion was based on incomplete data and was not reliable.

This study also identified that there remain substantive deficiencies in the statistics available on food supply and sugar consumption in Australia. To support measuring progress in achieving public health goals to reduce obesity, we recommend re-establishing the regular collection and production of a comprehensive suite of national statistics on the Australian food supply. A revision of classifications used to compile food statistics would also increase the quality of the available data.

Funders of the project: NHMRC program grant # 572742

METHODS FOR ENGAGING WITH THE COMMUNITY IN SETTING PRIORITIES FOR CHILD HEALTH RESEARCH

Wayne Rikkers, Katrina Boterhoven De Haan, David Lawrence, Anne McKenzie, Hayley Haines, Kirsten Hancock, Daniel Christensen and Stephen R. Zubrick

The vast majority of public health research in Australia is funded by the community. As there are more research ideas proposed than there are funds available, it is necessary to make choices as to which research will be provided funding. There is a recognised role for consumers and community members to participate in all phases of research, from choosing what to research through to translation of results. Many countries, including Australia, have formal policies and procedures for the involvement of consumers in health care planning and policy setting, however, models for consumer and community participation outside the health services research area are less well developed. This study aimed to evaluate and compare two different methods for obtaining community participation in a research field broadly described as human capability expansion, which encompasses several health as well as other disciplines, such as education and language development. As such, the entire community, not just those currently with young children would likely benefit from this research.

The Participation Program at the Telethon Kids Institute has developed a range of methods for fostering active involvement of community members in various stages of research. While their participation levels are good, their network represents a relatively small proportion of the Western Australian population. We wanted to test whether there were ways, other than the Institute's consumer and community consultation forums, called Community Conversations, of engaging with a broader cross-section of the community and if there were any differences in the views obtained using a different participation method and a larger sample of the population. We conducted a telephone survey of 800 randomly selected households across WA to seek people's views about our research program. We also ran two Community Conversations, one using the Participation Program to recruit participants, and the other using people recruited from the telephone survey.

We found that there was little difference in the views about our research expressed by participants from the Community Conversations compared with the respondents to the telephone survey. All respondents were very supportive of our work and were happy to allocate priorities to different areas of research. Generally, people were also in favour of community participation in the research process. However, there was a much higher proportion of females (78%) who participated in the phone survey than are in the general WA population (49.5%). Therefore, while the results showed that the Community Conversations attracted participants who are representative of those who are willing to give their views on our research via a telephone survey, we cannot be sure that the participants for either the Community Conversations or the telephone survey represent the whole community.

Funders of the project: NHMRC program grant # 572742

SUICIDALITY AND SOCIAL MEDIA

Francis Mitrou, Grant Smith, Monique Robinson and Kim Carter, with Simon Davies, Caroline Goossens, Amy Cleator and Siew Lan Ho (Western Australian Child and Adolescent Mental Health Services), Rosanna Capolingua (Western Australian Child and Adolescent Health Service) and Chris Harris (Youth Focus).

Child and Adolescent Mental Health Services (CAMHS) have noticed increasing admissions for self-harm with anecdotal evidence of a role for the internet and social media in supporting decisions to take self-harming action. This project seeks to develop a clinic based instrument to assess the influence of the internet and social media on each individual CAMHS presentation for self-harm. This instrument will be tested and refined in-service before being rolled out as a permanent tool for assessment across all CAMHS units.

Funders of the project: WA Department of Health

CONTRIBUTION OF INDIGENOUS CULTURAL FACTORS TO SURVEY RESPONSE

Francis Mitrou, with Paco Perales Perez and Bernard Baffour (The University of Queensland)

Some surveys are designed specifically to collect information from Indigenous populations, and these surveys accommodate Indigenous ways of understanding questions and response categories. When surveys are developed for the general population their design tends not to be tailored to Indigenous perspectives and ways of understanding. This may have implications for the survey results when general population surveys also collect information from Indigenous families that happen to fall under the sample capture. Where sample sizes allow, researchers often compare Indigenous to non-Indigenous outcomes as measured through general population surveys. This project asks whether such results could be misleading.

Funders of the project: ARC Centre of Excellence for Children and Families over the Life Course #CE140100027

INTERGENERATIONAL WELFARE DEPENDENCY IN AUSTRALIA

Stephen R Zubrick and Francis Mitrou with Paco Perales Perez, Angela Higginson, Janeen Baxter and Mark Western (The University of Queensland)

Intergenerational welfare dependency is a key component of deep persistent disadvantage. Documenting the situation in Australia is important to our understanding of the leverage points for policy action in the welfare space. This project will build on work started by this group prior to the advent of the Life Course Centre to understand the scale and nature of intergenerational welfare dependency in Australia, and will provide a basis for future research directions for The Centre.

Funders of the project: ARC Centre of Excellence for Children and Families over the Life Course #CE140100027

EVALUATION OF HEADSPACE (NATIONAL YOUTH MENTAL HEALTH FOUNDATION)

Francis Mitrou, Daniel Christensen, David Lawrence and Stephen R Zubrick with Ilan Katz, Kristy Muir and Fiona Hilferty (The University of New South Wales)

The Social Policy Research Centre (SPRC) at UNSW is under contract to the Australian Government Department of Health to deliver a broad ranging program evaluation of headspace. headspace has been operational since 2006 and is funded by the Department as part of a broader mental health service platform. To give an example of the scale of the program, headspace received operational funding of $81m for the 2012/13 financial year and will have 85 centres running nationally by mid-2015.

UWA have a sub-contract with SPRC to deliver the economic component of the headspace program evaluation. UWA are required to address three specific research questions:

1. What are of the costs and effects of the headspace program?
2. What is the overall cost effectiveness of expanding headspace beyond 100 centres?
3. What are the maximum funding requirements for headspace to achieve national coverage?

The project is due to be completed by May 2015.

Funders of the project: Australian Government Department of Health

TASMANIAN CHILD AND FAMILY CENTRES EVALUATION PROJECT

Cate Taylor, Sally Brinkman and Daniel Christensen with Wietse van de Lageweg, Andrew Oakley (Tasmanian Department of Education)

The specific aims of the Tasmanian Child and Family Centres (TCFC) evaluation project are to:

1. Establish the methodology for sustainable long-term process and impact evaluations of the TCFCs.

The development of a statewide evaluation plan is an important first step in setting up a sustainable long-term evaluation strategy for the TCFCs. The evaluation plan will identify the methodologies for evaluating the impact of the TCFCs on all measurable child, family, community and service outcomes in the Statewide Outcomes Framework.

2. Evaluate the short-term impact of the TCFC model on these direct family outcomes from the Statewide Outcomes Framework: Families are supported by and connected to their communities; parents have skills and knowledge to nurture their children; and families have opportunities to participate in learning pathways.

The TCFCs are newly established and need time to take effect before a broad impact evaluation can be conducted. It is hypothesised that the TCFC model will influence parental self-efficacy, access to training and connections to community services and supports in the short-term. Information about parent outcomes will be collected using survey methods. Outcomes for parents raising children in communities with a CFC will be compared to outcomes for parents raising children in communities without a CFC (i.e., usual care).

Funders of the project: Tasmanian Early Years Foundation

DEVELOPMENT OF THE ADOLESCENT SELF ESTEEM QUESTIONNAIRE

Katherine Hafekost, Katrina Boterhoven de Haan, and David Lawrence

Self-esteem impacts on many aspects of an individual's life. The current gold standard measure of self-esteem was developed in 1965. As a result, the language and concepts are somewhat out-dated. Therefore, for use in Young Minds Matter: The National Survey of Mental Health and Wellbeing, a contemporary measure of self-esteem was developed. The Adolescent Self-Esteem Questionnaire was specifically designed for young people and is intended to allow for more accurate assessment of self-esteem in research and practice. Ongoing work aims to determine the validity and reliability of the Adolescent Self Esteem questionnaire in a sample of young people to allow for the scale to be used in future research and practice.

Funders of the project: Australian Government Department of Health.

NATIONAL SURVEY OF MEDICAL PRACTITIONERS AND STUDENTS MENTAL HEALTH

Katherine Hafekost, David Lawrence and Stephen R Zubrick with Fei Wu and Michael Ireland (Roy Morgan Research)

The National Mental Health Survey of Doctors and Medical Students was conducted with the aims of determining the current mental health status of medical practitioners and students, gaining an understanding of associated issues within the medical and broader community,

and informing the development of mental health services and supports for this group. The project identified high levels of distress in both practitioners and students in comparison to the general population. In addition, practitioners and students reported high levels of depression, anxiety, burnout and thoughts of suicide. However, practitioners appeared to have a greater degree of resilience to some of the negative impacts of poor mental health with few doctors reporting being highly impacted by their mental health symptoms. Based on these findings, a number of recommendations were provided to beyondblue with the aim of improving the work experience, mental health status and coping ability of medical practitioners.

Funders of the project: beyondblue

TACKLING OVERWEIGHT AND OBESITY: DOES THE PUBLIC HEALTH MESSAGE MATCH THE SCIENCE?

Katherine Hafekost, David Lawrence, Francis Mitrou and Stephen R Zubrick, with Therese O'Sullivan (Edith Cowan University)

Despite an increasing understanding of the mechanisms which relate to weight loss and maintenance, there are currently no validated public health interventions which successfully achieve significant and sustained weight loss in the population. This project examined the model of energy balance which underpinned recent public health weight loss interventions and compared this to the model provided by basic sciences. It was identified that most public health interventions were based on an overly simplistic model of energy balance. It appeared that there was a lack of translation between advances in basic science and public health efforts to reduce excess weight. This project identified a need for a multidisciplinary approach in the design of future weight loss interventions in order to improve their long term success.

Funders of the project: NHMRC program grant #572742.

LIFE EXPECTANCY OF PEOPLE WITH MENTAL ILLNESS

David Lawrence and Kirsten Hancock, with Steve Kisely, The University of Queensland

People with mental illness are known to be at high risk for a range of common physical health problems. There are also well-documented inequities in levels of general medical care for people with mental illness. This study examined trends in life expectancy for people with mental illness in Western Australia.

The study used data from the WA Data Linkage System to compare mortality rates in people who have ever been treated for a mental health problem within a private or public hospital in Western Australia or at a mental health clinic, with the remainder of the population. About 5% of the WA population have received treatment for mental illness. Since 1985, the gap in life expectancy between people with mental illness and the remainder of the population increased from 13.5 years to 15.9 years for males and from 10.4 years to 12.0 years for females. While people with mental illness are at high risk of suicide, 80% of the excess deaths in people with mental illness were attributed to physical health conditions, principally cardiovascular disease, cancer and respiratory diseases.

Results from the study were presented to the Western Australian Clinical Senate in July 2013, and recommendations for changes in health care delivery, screening and preventative health care have been made to the Western Australian Department of Health.

Funders of the project: Griffith Institute for Health and Medical Research.

CANCER IN PEOPLE WITH MENTAL ILLNESS

David Lawrence, with Steve Kisely, The University of Queensland

People with mental illness are diagnosed with cancer at the same rate as the remainder of the population. However, people with mental illness are significantly worse survival after cancer diagnosis. This study set out to examine factors that may be associated with differences in outcomes after cancer diagnosis in people with pre-existing mental illness, including stage of cancer at time of diagnosis, use of chemotherapy and radiotherapy and surgical intervention.

The study used data from the WA Data Linkage System combining the WA Cancer Registry, the WA Hospital Morbidity Data System (which records all hospital admission in Western Australia, and the WA Mental Health Information System. The study found comparable rates of advanced cancers at first diagnosis, and comparable rates of use of chemotherapy and radiotherapy following diagnosis. However, people with mental illness were substantially less likely to undergo surgery to remove a tumour, particularly for breast cancer, prostate cancer and colorectal cancer where outcomes following surgery have been improving significantly in the general population.

Funders of the project: Cancer Council Queensland.

TRENDS IN ALCOHOL-RELATED HARMS FOLLOWING THE INTRODUCTION OF THE ALCOPOPS TAX

David Lawrence, with Steve Kisely, Angela White and Jason Connor, The University of Queensland

Alcopops are pre-mixed alcoholic beverages, predominantly spirit-based beverages with high alcohol content, that have been popular with young people. Following widespread public concern that these beverages encouraged higher alcohol consumption in young people, particularly women, the Australian Government introduced a 70% tax hike on alcopops in April 2008.

The purpose of this study was to use time series analysis methods to investigate if there was any change in rate of alcohol-related harms in Queensland following the introduction of the tax. The study used data from the Queensland Data Linkage System, including attendance at hospital emergency rooms, hospital admissions, and the Queensland Trauma Registry. The study was conducted in two phases. The first phase concentrated on emergency room attendances in the Gold Coast region, which is a high risk area for alcohol-related harms in young people, and the second phase examined data Queensland wide.

Both phases of the study found consistent results. Presentations at Emergency Rooms on the Gold Coast, and Queensland-wide, for alcohol-related injuries have been increasing at a steady rate among both males and females aged 15-29 years over the period of the study, which used data from 2006 onwards. The introduction of the alcopops tax was not associated with any change in the rate of increase in alcohol-related injuries resulting in emergency room attendance or hospital admission in Queensland, nor was there any change in serious alcohol-related injuries recorded on the Queensland Trauma

Registry.

While the alcopops tax may have had other benefits not measured in this study, the study has shown that alcohol-related injuries continue to be a major public health issue among young people.

Funders of the project: Population Health Research Network through the Australian Government's National Collaborate Research Infrastructure Strategy.

SMOKING AND MENTAL ILLNESS

David Lawrence, Francis Mitrou, Jennifer Hafekost, Cate Taylor and Stephen R. Zubrick, with Philip Hull (Cancer Council New South Wales), Michael Sawyer (University of Adelaide), Sharon Lawn (Flinders University), Ann Bates (Western Australian Mental Health Commission), Steve Kisely (The University of Queensland) and Julie Considine (Australian Bureau of Statistics)

Although smoking rates have fallen significantly since the 1960s, smoking and related-health impacts, remain a significant public health problem. This study has sought to quantify the role of mental illness in current smoking, and the possible benefits of considering the impact of mental illness in ongoing tobacco control activities.

In 2011-12, 20.4% of Australian males aged over 18, and 16.3% of females were current smokers. Over 80% of these smokers started smoking before age 15, and had become daily smokers by age 18. One-third of Australian smokers also have a mental illness, most commonly anxiety or depression, and these smokers smoke over 40% of cigarettes consumed in Australia. People with mental illness are more likely to start smoking at a younger age, find it more difficult to quit, smoke for longer, and as a result suffer more physical harm.

Mental illness has not been a major consideration in tobacco control in Australia or overseas. Some of the major tools used in tobacco control, such as advertising the long-term health effects of smoking, and stigmatising smoking behaviours are less motivating in people with mental illness. Even so, people with mental illness want to quit smoking, and try to quit smoking, as least as much as other smokers, but have substantially less success with their smoking cessation attempts.

Funders of the project: No specific funding received.

STATISTICAL METHODS TO MINIMISE DISCLOSURE RISK IN STUDIES USING LINKED ADMINISTRATIVE DATA

Katherine Hafekost, David Lawrence

Linked administrative data sets are becoming increasingly sought after for research and evaluation purposes. As the Western Australian Data Linkage System has grown in both size and scope, the number of requests for linked data extracts has been increasing. In considering requests for access to linked administrative data for research purposes, data custodians have the dual responsibility to maximise the amount of information available for research and analysis to improve knowledge, understanding and service delivery while minimising the risk of the privacy of individual's whose data are recorded within the system being violated. This project sought to identify possible statistical methods which minimise the risk while maximising data availability and utility.

The project aimed to determine whether samples of the full population data could be used to calculate accurate and reliable estimates of population parameters in analyses using data from the Western Australian Linked Data System. It was identified that this method was appropriate in some situations and ongoing work aims to determine whether this method can be used for more complex analyses.

Funders of the project: NHMRC program grant #572742.

PARENTING MEASURES IN THE LONGITUDINAL STUDY OF AUSTRALIAN CHILDREN: CONSTRUCT VALIDITY AND MEASUREMENT QUALITY, WAVES 1-4

Stephen Zubrick with Nina Lucas, Elizabeth Westrupp and Jan Nicholson

Project blurb: The LSAC mother- and father-reported parenting measures used across Waves 1 to 4 were examined to establish: a) the extent to which the items used to measure particular dimensions of parenting are reliable indicators of that construct; and b) the extent to which measures used at different ages appear to measure the same underlying construct. Initial model fitting revealed room for improvement across the majority of measures: 30% of the models exhibited a 'good' fit to the data, 38% were an 'acceptable' fit and 34% failed to meet the specified fit criteria. Model fits varied across waves and respondents. With only four exceptions, across 69 models minor modifications resulted in good (58%) or acceptable (36%) fit. We provide recommendations on the optimal approach for using the LSAC parenting measures in future analyses, including the use of item weightings and the exclusion of poorly performing items.

Funders of the project: Australian Government Department of Social Security

Research translated into articles in popular press

Farrant, B. M. (2013). Fragile progress in early childhood education could be undone. The Conversation. Retrieved from https://theconversation.com/fragile-progress-in-early-childhood-education-could-be-undone-19718

Farrant, B. M. (2013). Failing them badly: Who is protecting our children and grandchildren? Crikey. Retrieved from http://blogs.crikey.com.au/croakey/2013/02/11/as-energy-policy-threatens-our-health-who-cares-about-the-children-and-some-healthy-reading-on-climate-change/

Getting Our Story Right – the algorithm from this project has been adopted by the Department of Health for use to assist in addressing Indigenous under-identification in data linkage projects.

Student attendance and educational outcomes

In 2013, members of the Human Capability team released a research report that investigated the relationship between student attendance and performance on the National Program of Literacy and Numeracy (NAPLAN) tests for public school students in Western Australia. The research found that disparities in attendance rates, for example between disadvantaged and non-disadvantaged students, were evident as early as Year 1. The report also showed that there was no safe level of absence for students, and that every day of absence had an effect on NAPLAN scores, and for disadvantaged students in particular. Together, the results indicated that that the early years are a critical intervention point for improved attendance and achievement outcomes.

The report received great interest by researchers and state education departments across the country. Members of the research team have been invited to present the research to educators in Western Australia, Canberra,

Victoria and Queensland, discussing implications for attendance policy and the importance of the early years for establishing good attendance patterns. The Western Australia Department of Education, collaborators on the research, have found the research a valuable resource for their review of attendance policy for West Australian students. In further work, members of the team, in conjunction with the Department, are considering future possibilities for developing an intervention that helps to improve attendance for disadvantaged students. The research was also discussed with members of the community in a Community Conversation held at the Institute in August.

Playgroups

The Human Capability group, within the division of populations sciences, undertook research to determine if playgroup participation was associated with improved outcomes for children. The work showed that for children from disadvantaged backgrounds, those who had persistently attended playgroup across the early years had better social-emotional and cognitive outcomes at age 4-5 years than children who never participated in playgroup. The research has become a core part of lobbying and an essential reference in any explanation or literature of playgroups. Playgroup WA have used our findings in multiple presentations and funding applications, including a major attempt at lobbying the Federal Government and Opposition prior to and after the election and have been in ongoing discussions with the Department of Social Services (formerly FAHCSIA), and have also successfully lobbied to have playgroup participation included in the next AEDI checklist.

Infectious Diseases

THE KALGOORLIE OTITIS MEDIA RESEARCH PROJECT – AN INVESTIGATION INTO THE CAUSAL PATHWAYS TO OTITIS MEDIA IN ABORIGINAL AND NON-ABORIGINAL CHILDREN

Deborah Lehmann, Peter Jacoby, Wenxing Sun, Alicia Annamalay, Ruth Monck, Fiona Stanley, in collaboration with Bega Garnbirringu Health Services, Ngunytju Tjitji Pirni Inc, Harvey Coates, Christine Jeffries-Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane, Thomas Riley, Sharon Weeks, Allan Cripps, Jennelle Kyd, Jacinta Bowman, Gerry Harnett, David Smith, Glenys Chidlow, Denise Murphy, Kylie Carville, Stefano Occipinti, Amanda Leach, Nevada Pingault.

Otitis media (OM, middle ear infection) can seriously affect childhood development, school performance and subsequent social and economic well-being. The Kalgoorlie Otitis Media Research Project was established in 1999 to investigate the causal pathways to OM and, specifically, to identify demographic, socio-economic, environmental, microbiological and immunological risk factors for OM in Aboriginal and non-Aboriginal children in order to develop appropriate interventions. We followed 100 Aboriginal and 180 non-Aboriginal children from birth to age two years. Field work was completed in 2004 and data cleaning completed in April 2005. Analysis of association between bacterial carriage and mucosal immunity is ongoing.

Major findings

- The peak prevalence of OM in the Kalgoorlie-Boulder area was 72% in Aboriginal children aged 5-9 months and 40% in non-Aboriginal children aged 10-14 months.
- Almost one-third of Aboriginal children and 5% of non-Aboriginal children had a perforated ear drum at least once by age 2 years.
- 65% of Aboriginal children and 23% of non-Aboriginal children have some degree of hearing loss at age 12-17 months.
- Measurement of otoacoustic emissions in early infancy can identify children at subsequent risk of OM.
- Exposure to environmental tobacco smoke is an important risk factor for OM.
- Crowding is the strongest and most consistent predictor of carriage of OM-associated bacteria (pneumococcus, nontypeable Haemophilus influenzae, Moraxella catarrhalis) in the URT, but living in a larger house attenuates this effect in Aboriginal children.
- Daycare attendance predicts carriage of OM-associated bacteria in non-Aboriginal children while exclusive breastfeeding for the first 6-8 weeks of life protects children from carriage of Staphylococcus aureus.
- Rhinoviruses (HRV) and adenoviruses were commonly identified in asymptomatic children, more commonly in Aboriginal than non-Aboriginal children and are frequently associated with bacterial carriage.
- Human rhinovirus A is the most common virus type identified in healthy children and HRV C is associated with presence of upper respiratory symptoms and carriage of bacteria associated with OM.
- Early carriage of non-typeable H. influenzae increases risk of OM in Aboriginal children, while early carriage of M. catarrhalis increased risk of OM in non-Aboriginal children.
- A large proportion of M. catarrhalis strains were resistant to ampicillin and/or co-trimoxazole. Therefore, current therapeutic guidelines, which recommend amoxycillin for treatment of OM, may need to be revised. We have also documented for the first time simultaneous carriage of multiple strains of M. catarrhalis.

Funders of the project: Western Australian Health Promotion Foundation (Healthway); NHMRC Project Grant #212044 and as part of the NHMRC Program Grant #353514.

PREVENTING OTITIS MEDIA TO GIVE A SOUND START FOR SCHOOL (PINA PALYA PINA KULILKU, GOOD EARS GOOD LEARNING)

Deborah Lehmann, Ruth Monck, Wendy Sun, Lorraine Sholson, Fay Sambo, Kirsten Alpers, Tanyana Jackiewicz in collaboration with Anne Mahony, Charles Douglas, Michelle Forrest, Daniel McAullay, Bega Garnbirringu Health Services, Ngunytju Tjitji Pirni Inc, Francis Lannigan, Sharon Weeks, Bradley Gilchrist, Annette Stokes, Christine Jeffries-Stokes.

This 3-year project follows on from findings of the Kalgoorlie Otitis Media Research Project

in which we reported very high rates of otitis media (OM) and associated hearing loss, high carriage of bacteria in the upper respiratory tract (which predisposes to OM) from a very young age in Aboriginal children and an increased risk of OM among children exposed to environmental tobacco smoke. The overall aim is to have Aboriginal children hearing well by the time they start school.

The objectives of this project were to:

1. Develop and implement a multifaceted ear health promotion program in collaboration with Aboriginal organisations in the Goldfields.
2. Evaluate the impact and effectiveness of an ear health promotion program that includes (a) an awareness program, (b) training of health personnel in screening and health promotion and (c) a screening program for OM.
3. Evaluate use at primary health care level of a simple tool (which measures otoacoustic emissions) that can detect fluid in the middle ear at a very young age and hence identify a target group of children at subsequent risk of developing OM.
4. Evaluate the overall program in terms of feasibility and sustainability.

Over a 3-year period, we conducted 357 ear examinations in Aboriginal children under the age of 5 years. Of the 250 valid examinations, only half had bilateral normal middle ears; 15% had perforated ear drums which is often chronic and can lead to long term hearing loss. A total of 14 soap-making workshops were held in different communities. A series of music workshops, culminating in public performances of a musical, was conducted with school children at 5 locations to promote regular hand washing, keeping cigarette smoke away from children and regular ear screening. Since the launch of the Big Ear (an inflatable ear that children and adults can walk through) in February 2012, it has been used ~20 times at community events and schools.

As part of the evaluation of the Pina Palya Pina Kulilku project, we conducted interviews with members of the community at the start of the project and a research assistant who had not been involved in the study interviewed community members towards the end of the study period. At the end of the study period 56% had heard about the project and half of them had attended an activity. Twice as many people reported that ear disease can be prevented by not smoking around children and washing hands than at the start of the project. The project was well received by the community; they acknowledged that it helped to identify children with hearing problems early and they commented that the development of the musical through workshops was culturally appropriate and effective. Collaboration between different health service providers, education department and wider community has been greatly enhanced through the ear health project. A community report is in preparation.

NEONATAL IMMUNIZATION WITH PNEUMOCOCCAL CONJUGATE VACCINE IN PAPUA NEW GUINEA

Deborah Lehmann, Pat Holt, Peter Richmond in collaboration with Anita van den Biggelaar, William Saila Pomat, Peter Siba, Suparat Phuanukoonnon, Celestine Aho, Tilda Orami, John Reeder, Amanda Leach, David Smith, Ingrid Laing, Glenys Chidlow.

Throughout the world approximately 800,000 children die annually from pneumococcal disease, the majority in early infancy in third world countries. This study was designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in Papua New Guinean infants at 1-2-3 months of age and to find out whether neonatal immunisation in the first week of life would provide earlier protective antibody responses. We have assessed the impact of neonatal immunisation on humoral and cellular immune responses to concomitant vaccines (diphtheria toxoid, tetanus toxoid and measles) and whether PCV interferes with normal maturation of the immune system. A manuscript is in preparation on the impact of a 7-valent PCV (7vPCV) on early pneumococcal nasopharyngeal colonisation. Currently, we are investigating the impact of neonatal and early infant 7vPCV on pneumococcal serotype-specific mucosal immune responses. A total of 318 children were enrolled; 80% completed follow-up at 18 months of age. Results to date show

- No deleterious effect of neonatal 7-valent PCV (7vPCV).
- 7vPCV is immunogenic in PNG neonates and young infants.
- 7vPCV in a neonatal (0-1-2 months) or early infant (1-2-3 month) schedule primes for immunologic memory for 7vPCV serotypes with booster response to 23-valent pneumococcal polysaccharide vaccine (PPV) at age 9 months. Serotype-specific antibody concentrations are generally sustained to age 18 months.
- PPV induces good antibody responses for some non-PCV pneumococcal serotypes which commonly cause disease.
- 60% of infants were colonised with Streptococcus pneumoniae by age 1 month.
- 54 different pneumococcal serotypes have been identified in the upper respiratory tract.
- At age 9 months, 68-78% of pneumococci in the upper respiratory tract were non-7vPCV serotypes.
- At age 9 months, non-7vPCV serotypes are more commonly carried in the upper respiratory tract of children who received 7vPCV than in controls.
- Early pneumococcal carriage may result in enhanced disease susceptibility and suboptimal vaccine responses by modulating the development of pneumococcal immune responses.
- Analysis of cellular immune responses has shown that neonatal PCV vaccination is safe and not associated with immunological tolerance.
- Analysis of saliva samples shows that 7vPCV generally primes mucosal immune responses for boosting by pneumococcal polysaccharide vaccine at age 9 months

In an extension of this project IA Laing investigated the contribution of human genetic susceptibility to nasal bacterial carriage,

development of immune/vaccine responses and the incidence of pneumonia in this population. Preliminary results from investigation of associations between genotype and acute lower respiratory infections (ALRIs) suggest that several genetic variants for known immune pathways may play a role in the frequency of lower respiratory tract infections in children in PNG.

Funders of the project: This study was funded by the NHMRC/Wellcome Trust International Collaborative Research Grant #303123. Optimisation of mucosal immunity assays in PNG funded by Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant.

INVESTIGATION OF SEROTYPE-SPECIFIC ANTIBODY PERSISTENCE AND B-CELL MEMORY AT AGE 3 - 4 YEARS FOLLOWING 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE AT AGE 9 MONTHS IN PAPUA NEW GUINEAN CHILDREN PREVIOUSLY PRIMED WITH 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

Peter Richmond, Deborah Lehmann, Peter Jacoby, Anita van den Biggelaar, Angela Fuery in collaboration with Peter Siba, William Saila Pomat, Andrew Greenhill, Christine Opa, Gerard Saleu

Recently, concerns have been raised about the role of the 23-valent pneumococcal polysaccharide vaccine (PPV) in infants following priming with a pneumococcal conjugate vaccine due to a potential immunological hypo-responsiveness (i.e. a poorer immune response to subsequent immunisation or natural exposure). In PNG we previously found that (a) PPV given from age 6 months onwards (without priming with conjugate vaccine) prevents death and severe morbidity due to acute lower respiratory tract infections up to age 5 years and (b) serotype-specific pneumococcal antibody responses are generally sustained up to age 18 months with a PPV booster at age 9 months following priming with 3 doses of 7vPCV. Nevertheless it is important to ensure the immunological safety of the PPV in infants.

This study aims to determine whether PPV given at 9 months of age:

1. provides enhanced persistence of antibody levels associated with protection from invasive disease at 3 to 5 years of age compared to unvaccinated controls
2. has an impact on the development of serotype-specific B-cell memory at 3 to 5 years of age
3. enhances antibody persistence and B-cell memory for those serotypes included in 7vPCV among children who received 7vPCV in early infancy
4. has an effect on long-term pneumococcal carriage in children primed or not primed with 7vPCV

We are assessing immune function (by measurement of serotype-specific antibody concentrations, opsonophagocytic antibodies and memory B-cell responses) and nasopharyngeal carriage at age 3-5 years prior to and one month after a challenge dose (0.1ml) of PPV in children who took part in the previous neonatal 7vPCV trial (described above) and in 150 age-matched controls. We enrolled 130 of the children who had previously received PPV (primed or not primed with 7vPCV) and 150 controls.

Key findings are:

- Pneumococcal carriage rates remain high to age 5 years (>70%, predominantly non-7vPCV serotypes) irrespective of vaccination history.
- Post-challenge dose, serotype-specific IgG antibody levels are generally higher than pre-challenge levels.
- Increasing pre-challenge IgG concentrations is associated with a decreased IgG response to challenge in both PPV-vaccinated and unvaccinated children.
- Prior receipt of PPV was not associated with reduced IgG response to PPV challenge dose
- Memory B-cell responses to challenge dose at 3-5 years were similar in children given PPV at 9 months compared to that in unvaccinated children
- Hypo-responsiveness after PPV may be less likely in children with high carriage rates

Funders of the project: Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant and Merck Sharp & Dohme

A STUDY TO DETERMINE THE SAFETY AND IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES IN PAPUA NEW GUINEAN CHILDREN

Deborah Lehmann, Andrew Greenhill, Peter Richmond, Lea-Ann Kirkham in collaboration with Peter Siba, William Saila Pomat, Audrey Michael (deceased), Celestine Aho, Vela Solomon, William Lagani, Trevor Duke, Megan Passey

Throughout the world approximately 800,000 children die annually from pneumococcal disease, the majority in early infancy. Pneumococcal conjugate vaccines (PCVs) have been introduced into routine immunization programs in many industrialised countries and an increasing number of third world countries, and 23-valent pneumococcal polysaccharide vaccine (PPV) has been shown to prevent death and severe disease from age 6 months onwards in Papua New Guinea (PNG). The Global Alliance for Vaccines and Immunisation (GAVI) and the World Health Organization (WHO) have committed to the introduction of PCV for infants in GAVI-eligible countries (including PNG). No pneumococcal vaccine was available in PNG until 13vPCV was introduced in November 2013.

The primary aim of this study, which began in November 2011, is to determine whether PCV10 and PCV13 (which include 10 or 13 pneumococcal serotypes, respectively) are safe and immunogenic in Papua New Guinean infants for the serotypes in the respective vaccines.

This is an open randomised trial. We aim to enrol 260 children at age 1 month. Half are randomised to receive PCV10 and the other half PCV13 in a 1-2-3-month schedule. At age 9 months half in each group are randomised to receive 23vPPV and the other half no

PPV. To specifically address the possibility of hyporesponsiveness following PPV, all children will receive a challenge dose (0.1ml) of PPV at age 23 months and followed up 4 weeks later. Pernasal swabs to investigate upper respiratory tract carriage and blood for antibody studies and measurement of B- and T-cell responses are collected at ages 1, 4, 9, 10, 23 and 24 months of age. By the end of 2013, 241 children were enrolled in the study and 739 pernasal swabs and 731 blood samples have been collected.

To date we have analysed blood samples collected pre-PCV and 1-month post-3rd dose PCV from 77 children who received 10vPCV and 68 who received 13vPCV. We have found that early schedules of PCV10 and PCV13 are immunogenic in PNG infants, inducing comparable antibody levels and achieving high protective antibody levels at age 4 months.

Funders of the project: Exxon-Mobil Governance and Public Affairs and Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant.

MONITORING CARRIAGE OF STREPTOCOCCUS PNEUMONIAE AMONG ABORIGINAL CHILDREN AND ADULTS IN WESTERN AUSTRALIA

Deborah Lehmann, Anke Hoskins, Deirdre Collins, Janice Lim, Kalpani Senasinghe, Peter Richmond in collaboration with Jacinta Bowman, Natalie Thomsen, Tom Riley, Carolien Giele, Paul Effler, Amanda Leach.

Streptococcus pneumoniae (pneumococcus) can cause middle ear infections and invasive pneumococcal disease (IPD) resulting in meningitis, pneumonia and septicaemia (blood poisoning). The Australian Aboriginal population has among the highest reported IPD rates worldwide. The existence of over 90 known types (serotypes) of pneumococci increases the challenge of prevention. A pneumococcal conjugate vaccine (Prevenar-7™, PCV7) covering the 7 most common serotypes causing IPD was offered to Aboriginal children from 2001 to 2011 in a 2-4-6-month schedule. A pneumococcal polysaccharide vaccine (Pneumovax™) covering 23 serotypes is offered to adults. While there has been a marked reduction in IPD due to the near elimination of Prevenar-7™ serotypes, in the 2000s there was an increase in IPD rates, particularly in young Aboriginal adults, due to serotypes not included in the vaccine. In light of this, Prevenar-7™ was replaced with Prevenar-13™ on 1 July 2011, which covers six additional serotypes.

Pneumococci are carried in the back of the nose of healthy as well as sick individuals and the acquisition of pneumococci is prerequisite to develop disease. Surveillance of pneumococcal carriage offers important complementary information to data on IPD since it can quickly provide a large amount of information on serotypes circulating in the population. It also gives a conservative estimate of antibiotic resistance of invasive pneumococcal strains.

This study aims to monitor the impact of different versions of PCV on pneumococcal carriage by collecting pernasal swabs opportunistically from Aboriginal adults and children in urban, rural and remote areas of Western Australia. We also collect ear swabs from children with middle ear discharge and data on vaccination status of children in the study.

Other study aims include:

1. Describing the prevalence of upper respiratory tract (URT) carriage of other pathogens identified on primary culture, in particular non-typeable Haemophilus influenzae and Moraxella catarrhalis which cause otitis media
2. Comparing the distribution of pneumococcal serotypes in the URT with those causing IPD in Aboriginal adults and children annually
3. Monitoring antibiotic resistance pattern of pneumococci
4. Storing pernasal swabs for detection of viruses by PCR to describe the prevalence of respiratory viruses and
5. Investigating viral-bacterial interactions in the URT.

To date we have collected ~2780 pernasal swabs and 50 swabs of discharge from the middle ear.

Pneumococcal carriage rates dropped slightly after the introduction of Prevenar-13™ but remain high in young children, being highest in the 6-23month age group (~70- 80%). More than 60% of children <6 months of age carried pneumococci. .

In children under 5 years of age nontypeable Haemophilus influenzae and Moraxella catarrhalis were each isolated from 63% of pernasal swabs. In people aged ≥5 years 22% grew nontypeable Haemophilus influenzae and 27% grew Moraxella catarrhalis. Since 2008 forty five different pneumococcal serotypes were identified in 1123 pneumococcal positive swabs. Currently, the most common pneumococcal serotypes in children <5 years of age are 19F, 6C and 16F while 19F, 10A and 15B are most common in older children and adults. It is noteworthy that carriage of 19F remains common despite its inclusion in both PCVs. There has been some reduction in carriage of serotypes included Prevenar-13™ since its introduction.

Surveillance of pneumococcal carriage is ongoing.

A paper describing nasopharyngeal carriage in the WA Aboriginal population was published in 2013 and a paper investigating risk factors for pneumococcal carriage is in draft form.

Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation (CARE) and NHMRC Project Grant #545232 (a collaboration with the Menzies School of Health Research).

INVESTIGATING THE RISK FACTORS AND CO-MORBIDITIES ASSOCIATED WITH INVASIVE PNEUMOCOCCAL DISEASE IN THE WESTERN AUSTRALIAN POPULATION

Deborah Lehmann, Faye Janice Lim, Hannah Moore, in collaboration with Catherine Harrison, Judith Willis, Aoiffe McLoughlin, Carolien Giele and Anthony Keil.

Invasive pneumococcal disease (IPD) refers to disease that occur when Streptococcus pneumoniae invades a normally-sterile site (e.g. cerebrospinal fluid or blood stream). Vaccines targeting S.pneumoniae are currently available

in Australia. We investigated the risk factors and comorbidities present in people with IPD in Western Australia. We found that approximately 65% of IPD cases were adults (aged 15 years or more) and the majority of IPD cases were diagnosed with pneumonia. The most common comorbidity in non-Aboriginal adults were cardiovascular disease and chronic respiratory infection. In Aboriginal adults, the most common risk factors were smoking and excessive alcohol use. Of the adults with risk factors who were eligible for vaccination and for whom we had vaccination status, more than 75% were not vaccinated.

The Vaccine Impact Surveillance Network (VISN) conducted enhanced surveillance on Invasive Pneumococcal Disease (IPD) between 1996 and 2007. Everyone is susceptible to IPD, though most at risk are children under the age of 2 years, elderly persons and those with chronic disease and compromised immune systems. The Australian Aboriginal population has among the highest reported IPD rates worldwide and incidence rates in this population are higher across all age groups than in non-Aboriginal people. Since January 2008, the Communicable Diseases Control Directorate (CDCD) has conducted the surveillance of IPD across Western Australia. Our previous publications reported on the incidence and serotype distribution of IPD notifications in the WA Aboriginal and non-Aboriginal population. This project involves analysis of the IPD surveillance data between 1997 and 2007 to investigate the underlying co-morbidities and risk factors associated with IPD. We aimed to describe the clinical diagnosis, co-morbidities reported in IPD cases according to age, gender, geographical region and Aboriginal status. Major findings are:

- Approximately 65% of IPD cases occurred in adults aged ≥15 years.
- Pneumonia was the most common diagnosis (61% of non-Aboriginal, 49% of Aboriginal adult IPD cases).
- In non-Aboriginal children aged < 5 years, congenital abnormality was the most common while in their Aboriginal counterparts chronic respiratory disease was most common in Aboriginal children aged < 5 years.
- Cardiovascular disease and chronic respiratory disease were the most common co-morbidities in non-Aboriginal adults aged ≥15 years.
- Smoking and excessive alcohol use were the most common risk factors in Aboriginal adults aged ≥15 years.
- Smoking was the most common risk factor in Aboriginal and non-Aboriginal adults up to 50 years of age.
- 41% of non-Aboriginal and 60% of Aboriginal children were eligible for vaccination but were not vaccinated
- Among adults with risk factors, eligible for vaccination and with known vaccination status, more than 75% were not vaccinated.

Analyses for this project have been completed. An advanced draft of the manuscript is being prepared for publication. Study findings have been presented at the National Indigenous Immunisation Workshop (Fremantle, 7-8th November 2013) and the 8th World Congress of the World Society for Paediatric Infectious Diseases (Cape Town, South Africa, 19-22nd November 2013).

Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation and the Meningitis Centre.

EXAMINING STREPTOCOCCUS PNEUMONIAE COLONISATION IN YOUNG CHILDREN IN WESTERN AUSTRALIA (URBAN PNEUMOCOCCAL COLONISATION PROJECT)

Christopher Blyth, Deborah Lehmann, Paul Effler, Peter Richmond, Anke Hoskins, Kalapani Senasinghe

Following introduction of 13-valent pneumococcal vaccine, it is expected that non-vaccine preventable pneumococcal serotypes will emerge. To determine the possible emerging pneumococcal serotypes, pneumococcal strains colonizing the nasopharynx of young children will be identified from nasopharyngeal swabs. Swabs are currently taken from children presenting for immunization at the Central Immunisation Clinic, Rheola Street. To date, more than 600 children have been enrolled with pneumococci detected in 20% of those enrolled. Culture and serotyping is currently being performed.

Streptococcus pneumonia is the most common bacterial cause of pneumonia and meningitis in WA. Following the introduction of pneumococcal vaccines in 2005, a number of strains of the bacteria emerged that were not protected by the vaccine. Following introduction of a new vaccine in 2011, we expect that further strains will emerge. This project will identify these emerging strains by detecting what strains are present in immunised and non-immunised children

Funders of the project: WA Department of Health

THE AETIOLOGY OF ACUTE LOWER RESPIRATORY TRACT INFECTION AND MENINGITIS IN HOSPITALISED CHILDREN FROM THE EASTERN HIGHLANDS PROVINCE, PAPUA NEW GUINEA

Christopher Blyth, Lea-Ann Kirkham, Deborah Lehmann and Peter Richmond in collaboration with Willie Pomat, Andrew Greenhill, Rebecca Ford, Paul Horward, Ilomo Hwaihwanje, Celestine Aho, Wapling, Yazid Abdad, Peter Siba, Laurens Manning and Trevor Duke

Pneumonia and meningitis are common and serious diseases of childhood, with significant morbidity and mortality among children under five years of age, particularly in third world settings. Streptococcus pneumoniae and Haemophilus influenzae type B (Hib) together are estimated to account for two-thirds of pneumonia and meningitis deaths among children under five. Hib vaccination was introduced in Papua New Guinea in 2008. The Global Alliance for Vaccines and Immunisation (GAVI) and the World Health Organization (WHO) have committed to introduce pneumococcal conjugate vaccine for infants in PNG in 2014.

The primary aim of this study is to determine the bacteria and viruses responsible for childhood pneumonia and meningitis in PNG. In addition,

we will determine which pneumococcal serotypes colonise the nasopharynx and result in invasive disease. Moreover, we will determine the frequency of antibiotic resistance to guide national empiric antibiotic guidelines.

Commencing in January 2013, 309 cases and 180 controls have been recruited in the first year of the study. To date, only 5 children with confirmed pneumococcal pneumonia, 4 children with confirmed Haemophilus influenzae type b pneumonia and 1 child each with pneumococcal and Haemophilus influenzae type b meningitis have been identified. Recruitment is ongoing.

Funders of the project: Pfizer Global and Papua New Guinea Institute of Medical Research

VALIDATING AND ENHANCING POPULATION-BASED DATA LINKAGE FOR INFECTIOUS DISEASE RESEARCH

Hannah Moore, Christopher Blyth, Faye J Lim, Beverly Valenti

Acute lower respiratory infections (ALRI) are a major cause of childhood morbidity, with higher rates of infection in Aboriginal children. It is a recommendation for children hospitalised with ALRI to have a laboratory investigation to determine the causative pathogen. This is essential to guide clinical management of the patient and to monitor temporal trends in specific pathogens which aid in vaccine policy development. Using population-based data linkage, only 50% of hospitalisations in metropolitan WA linked to a laboratory record from 2000-2005. Linkage was particularly low in non-metropolitan areas: <5% of hospitalisations in some remote areas linked and <10% in rural areas. Given the low levels of laboratory data linkage across WA, we thought it was crucial to determine the validity of our linked data and determine whether children are either being under-investigated for respiratory pathogens or there are deficiencies within our data linkage extraction protocols. We developed a medical chart review to be conducted in 7 hospitals across WA. The primary purpose was to document the proportion of ICD10-coded hospitalisations for ALRI that had any microbiological investigations.

A data collection sheet was designed to capture microbiological investigations, reported comorbidities, radiological investigations and details of clinical management. The hospitals chosen for this review were: Princess Margaret Hospital for Children (PMH), Fremantle Hospital and Joondalup Health Campus to represent metropolitan WA; Geraldton Hospital and Bunbury Regional Hospital to represent rural WA and Broome Hospital and Derby Hospital to represent remote WA. These hospitals were chosen as they represent 57% of all hospitalisations for respiratory infections in WA and showed varying proportions of records that linked to laboratory data. In total 766 medical charts were selected for review. By December 2013, data collection had been completed for 82% of records. Preliminary results show that the frequency of microbiological investigations was higher than our estimates from linked data. Overall 465 (74.2%) of admissions had evidence of laboratory investigations, most commonly a nasopharyngeal aspirate/nasal swab (NPA) and/or a blood culture. Frequency of testing varied by site with a high frequency of testing at PMH (92.5%) and Joondalup (96.7%) and low frequency of testing at Geraldton (34.7%) and Derby (48.3%).

It is a recommendation for children requiring hospitalisation with a chest infection (like bronchiolitis or pneumonia) to have a laboratory test. From our previous work, where we brought information about hospital and laboratory records together through data linkage, we found that few children, especially those in rural and remote hospitals of Western Australia, had a laboratory test. This project will involve going around to various hospitals and manually checking their records to see how many children did have a laboratory test. This will help us determine whether our previous data linkage work was inaccurate, or whether children are being under-investigated for chest infections.

Funders of the project: TICHR Small Grant

AETIOLOGY, BURDEN AND CAUSAL PATHWAYS OF ACUTE LOWER RESPIRATORY INFECTIONS USING POPULATION LINKED DATA

Hannah Moore, Deborah Lehmann, Peter Jacoby, Nicholas de Klerk in collaboration with Peter Richmond, David Smith, Anthony Keil, Christopher Blyth.

Acute lower respiratory infections (ALRI), or chest infections like influenza and pneumonia, are a major cause of illness in young children. The primary objective of this project was to describe the aetiology, burden and causal pathways of ALRI in Aboriginal and non-Aboriginal children from a 10-year birth cohort (245, 249 births from 1996 to 2005) using population-based linked data from the Western Australian Data Linkage System. Datasets include the Midwives' Notification System, Hospital Morbidity Database System, Birth and Death Register, Emergency Department Data Collection, Birth Defects Register and the PathWest Laboratory Database. This project was the first to link statewide laboratory data for respiratory pathogens to other datasets within the Western Australian Data Linkage System. This project concluded in 2013. The key findings which have been presented in many local, national and international forums and peer-reviewed manuscripts include:

- Hospitalisations for all-cause pneumonia in Aboriginal children fell by 28-44% in 2001-2005 compared to 1996-2000. The resultant disparity for pneumonia hospitalisation between Aboriginal and non-Aboriginal children fell by a third.
- Male gender, being born in autumn and multiple pregnancies are risk factors for hospitalisation for ALRI in both Aboriginal and non-Aboriginal children <2 years.
- Children born by elective caesarean are at increased risk of hospitalisation for bronchiolitis.
- Respiratory syncytial virus (RSV) was the most commonly identified respiratory pathogen, identified in >39% of hospitalisations.
- Children born with birth defects have a two-fold higher rate of hospitalisation for ALRI in the first 2 years of life than children without birth defects.
- Presentations to metropolitan emergency department for ALRI are high, especially

for croup and bronchiolitis, however are minimum estimates due to the current limitations of the ED datasets.

- Some respiratory pathogens could be identified across a range of diagnosis codes, indicating that reliance on diagnostic codes could underestimate the true burden of pathogen-specific ALRI.
- Seasonality for bronchiolitis and RSV-related hospitalisations varies between different health regions in WA and as such, localized immunoprophylaxis schedules are required.

Lower respiratory, or chest infections, are a problem for many children. This project investigated the impact of chest infections on hospitals and emergency departments, the viruses and bacteria that cause them and identified those groups of children who are at an increased risk of having a chest infection. This project has greatly added to our understanding of chest infections and has formed the basis for further studies.

Funders of the project: NHMRC Project Grant APP572590.

HOSPITALISATION FOR DIARRHOEA AMONG WESTERN AUSTRALIAN CHILDREN

Hannah Moore, Deborah Lehmann, Faye J Lim in collaboration with Karthik Manoharan, Geoff Shellam.

Diarrhoea is a significant reason for hospitalisation in Australian children. This study utilising total population-based data from the Maternal and Child Health Research Database investigated the trends in hospital admissions for diarrhoeal diseases (gastroenteritis) in Western Australian children aged <15 years between 1983 and 2006. Gastroenteritis rates were highest in children 6–11 months of age (Aboriginal: 259.3/1000/annum; non-Aboriginal: 22.7/1000/annum). Rates declined in Aboriginal children between 1983 to 1994 and 1995 to 2006, particularly in those 12–17 months of age (309/1000 to 179/1000). Rates in non-Aboriginal children aged <5 years increased 10–40%. The disparity for gastroenteritis rates between Aboriginal and non-Aboriginal children declined from being 15.4 times higher to 7.6 times higher in those aged 12–17 months and from 8.4 to 4.4 times higher in those aged 2–4 years. Rates were highest in rural and remote regions, and diverging temporal trends were seen in different geographical regions. Seasonality varied between Aboriginal and non-Aboriginal children and climatic zones. This was the largest study of gastroenteritis hospitalization trends in children. Our findings highlight the need to consider age, ethnicity, seasonality and climate when evaluating rotavirus vaccine programs. The findings of this study were presented at the 8th World Congress of the World Society for Paediatric Infectious Diseases, November 2013 in Capetown, South Africa and were published in the The Pediatric Infectious Disease Journal.

Gastroenteritis, or diarrhoea, is a major reason for children to be admitted to hospital. We undertook the largest study in the world to describe how many Aboriginal and non-Aboriginal children were admitted to hospital for diarrhoea and how this has changed over the past 20 years. We found that the number of Aboriginal children being admitted to hospital per population had declined while number of non-Aboriginal children per population has slightly increased. This project has provided us with good background information to be able to evaluate the rotavirus vaccine program that was introduced in 2007 to reduce the burden of diarrhoea.

Funders of the project: NHMRC Program Grant APP353514.

USING TOTAL POPULATION DATA TO DESCRIBE THE CHARACTERISTICS OF RESPIRATORY INFECTIONS IN ORDER TO PREDICT FUTURE EPIDEMICS AND RECOMMEND VACCINATION STRATEGIES FOR WESTERN AUSTRALIAN CHILDREN

Hannah Moore, Nicholas de Klerk, Peter Jacoby in collaboration with Geoff Mercer, Alexandra Hogan, Katie Glass

Respiratory Synctial Virus (RSV) is the most common pathogen found in infants and young children who are admitted to hospital. RSV is predominantly associated with bronchiolitis and pneumonia. There is currently no licensed vaccine for RSV, but immunoprophylaxis, or passive immunisation, with RSV monoclonal antibody, Palivizumab, is effective in reducing RSV related illness when administered monthly during the peak times of RSV activity. This is traditionally between May and October. However, Western Australia covers several climatic zones from tropical in the north to temperate in the south. Furthermore, an attenuated intranasal RSV/PIV3 vaccine (MEDI-534) is currently undergoing Phase I and II trials in infants and young children. In view of this, appropriate vaccination strategies need to be developed now and be in place when this vaccine becomes available. Currently still unknown are the seasonal characteristics of RSV in rural and remote Western Australia and whether there are differences according to Aboriginality, age group and other demographic characteristics or risk factors. Research into these areas is needed in order to maximise our understanding of the flow of these infections through the population as a whole.

Characterising the annual epidemics of respiratory infections can be achieved through mathematical modelling of virus transmission dynamics. These models aim to mathematically describe the flow of individuals in a population through a pre-infectious (susceptible) state, infectious state and then recovered or immune state. They can be used to characterise seasonal epidemics of pathogens by estimating and predicting transmission parameters such as the average duration of infectiousness or the force of infection (defined as the rate at which susceptible individuals become infected). Models can then be used to measure the likely impact of intervention programs (eg vaccination or school closures) and determine the optimum timing of interventions and the proportion of the population that need to be vaccinated in order to reach the herd immunity threshold. To improve the accuracy of mathematically generated models, real population data are needed. This project uses our unique linked laboratory, birth cohort and hospitalisation dataset of births in Western Australia between 2000 and 2005. We have constructed a mathematical model to accurately mimic the alternating seasonal peaks of RSV

detections seen in metropolitan Western Australian children. This base model can now be used to explore aspects of the seasonality of RSV in different risk groups and estimate the impact of a newborn vaccination program. Our first publication from this project is currently undergoing a second round of peer review with Plos ONE.

Respiratory Syncytial Virus (RSV) causes considerable illness in children. There is no vaccine for RSV and many of the characteristics of RSV are unknown. This projects uses data collected from a previous study that brought together information on RSV from various sources. We have constructed a mathematical model that mimics the seasonal patterns of RSV seen in metropolitan children of Western Australia. Now that we have a base model, we can explore certain characteristics of RSV, such as the differences in patterns of RSV in tropical climates of Western Australia.

Funders of the project: NHMRC Early Career Fellowship (HM) APP1034254.

LINKAGE OF THE AUSTRALIAN CHILDHOOD IMMUNISATION REGISTER (ACIR) AND STATE-BASED REGISTERS TO EVALUATE AND INFORM AUSTRALIA'S IMMUNISATION PROGRAM

Hannah Moore, Christopher Blyth, Nicholas de Klerk, Peter Richmond in collaboration with Heather Gidding, Bette Liu, Peter McIntyre, Louisa Jorm

Infectious diseases are the most common reason for children to be admitted to hospital. Immunisation represents the most important public health intervention to prevent infection. Despite the success of immunisation programs, outbreaks of vaccine-preventable diseases such as pertussis (whooping cough) continue to occur, with Aboriginal and Torres Strait Islander children, those living in remote areas, and those with underlying illnesses suffering a disproportionate burden of preventable disease. Accurate information on whether children are being vaccinated, the timing of their vaccination and how well the vaccines are working to reduce disease in the community overall, and in specific populations are required. Currently, this information is derived from stand-alone databases such as the Commonwealth funded- Australian Childhood Immunisation Register (ACIR) and compared to separate state-based databases of disease notifications or hospitalisations. While analysing these datasets in isolation is useful, their linkage would allow more accurate studies on the relationship between vaccination, timeliness of vaccination, and development of disease in various population sub-groups.

This study proposes to link data that are stored on administrative databases for children born in NSW and WA from 2000 to 2012. We will link the following records: births and deaths, immunisation, hospitalisation, emergency department visits, and infectious disease notifications (e.g. whooping cough, pneumococcal disease and influenza). By bringing together all this information, we aim to:

- Determine whether there are particular characteristics that identify children who are not receiving vaccinations on time;
- Calculate the effectiveness of vaccinations in reducing disease;
- Compare the effectiveness of vaccinations in reducing disease between different risk groups, over time, and between NSW and WA.

In 2013, multiple ethical approvals and data custodian approvals were obtained from Western Australia, New South Wales and the Commonwealth. We anticipate that the linked data will be received by the project team in 2014.

In order to optimise the health and cost benefits of Australia's immunisation program, accurate data are required about how well the program is performing. Currently, information about this is limited. In this study we will for the first time bring information together for a population of births in WA and NSW on immunization records, hospital admissions, disease notification records, laboratory records and birth records. We will use this information to accurately determine how many infants and children are receiving their recommended vaccinations on time and if they are working to reduce the amount of infections that infants and young children suffer.

Funders of the project: Population Health Research Network Proof of Concept #4 Project.

IDENTIFYING OPPORTUNITIES FOR PREVENTING RESPIRATORY INFECTIONS IN CHILDREN THROUGH INTEGRATING POPULATION-BASED HEALTH AND LABORATORY DATA

Hannah Moore, Christopher Blyth, Peter Jacoby, Faye Janice Lim, Parveen Fathima

Acute lower respiratory infections (ALRI), or chest infections, such as bronchiolitis, influenza, pneumonia and whooping cough are a major cause of morbidity in children. ALRI is the most common reason for hospitalisation in children aged less than 2 years and contributes to approximately 10,500 days in hospital per year in children aged less than 5 years with a peak in the winter months. Costs associated with ALRI admission in children are also substantial. Although there has been some improvement in the incidence of ALRI in Aboriginal children, there is still a disproportionate burden compared with non-Aboriginal children. One in four Aboriginal children, compared to one in 15 non-Aboriginal children, are hospitalised for ALRI in Western Australia (WA) before age five years.

The pathogens most commonly associated with ALRI include respiratory syncytial viruses (RSV), influenza viruses, parainfluenza viruses, rhinoviruses, adenoviruses, Streptococcus pneumoniae and Bordetella pertussis. Some pathogens are found simultaneously in children with ALRI (known as co-infection). The impact of co-infection on clinical severity outcomes (such as hospital length of stay and admission to intensive care units) is unknown. The most effective prevention of ALRI is vaccination, although vaccines are only currently available for a selection of known ALRI pathogens. Furthermore, most available vaccines only target specific strains of a pathogen. Over time, non-vaccine strains may replace those strains for which vaccines are available. Therefore it is important to regularly monitor changes in pathogen-specific trends of ALRI to increase our understanding of the local epidemiology of ALRI in order to recommend, develop and implement

appropriate vaccination programs. Furthermore, due to the nature of co-infection, it is important to monitor changes in the epidemiology of ALRI due to replacement of pathogens following vaccination of another pathogen. Individual-based data linkage of routinely collected laboratory data, infectious disease notification data and hospital and emergency department presentation data on a total population basis allows these investigations to take place.

This proposed project will investigate pathogen-specific hospitalisations and emergency department presentations for ALRI between 1996 and 2011 (or most recent data at time of extraction) and will further investigate the impact of co-infection. The specific aims of this project are:

1. To quantify the pathogen-specific burden of ALRI in WA using individually-linked laboratory, hospitalisation, emergency department and disease notification datasets.
2. To assess the impact of viral-viral and viral-bacterial co-infections on ALRI outcomes and document the relative contribution of individual respiratory pathogens to these outcomes.
3. To evaluate the positive and negative, direct and indirect, population impact of paediatric immunisations on hospitalisations and emergency department presentations for ALRI, ALRI-related conditions or vaccine-preventable infections by conducting pre- and post-vaccination introduction temporal trend analyses.
4. This project will complement the national study funded through the Population Health Research Network between WA and New South Wales (through collaborations with the University of New South Wales and the National Centre for Immunisation Research and Surveillance) to investigate the vaccine effectiveness of vaccine-preventable diseases. This will be conducted through the linkage of immunisation data from the Australian Childhood Immunisation Register.

In 2013, ethical approvals and data custodian approvals were obtained from all relevant ethics bodies and custodians. We anticipate that the linked data will be received by the project team in 2014.

Chest infections, like influenza and pneumonia, are a major cause of illness in children. By bringing together information that is stored on public records, we will describe the viruses and bacteria that are associated with chest infections in Western Australian children over a 16 year period. We will look at how multiple infections (when two or more viruses or bacteria are found at the same time) affect the severity of illness. We will investigate if vaccines designed for chest infections have reduced hospital and emergency department visits. This information will identify opportunities where we can reduce the number of children affected by chest infections.

Funders of the project: NHMRC Project Grant APP1045668

THE PATHOGEN SPECIFIC BURDEN OF HOSPITALISATION FOR ENTERIC AND BLOOD STREAM INFECTION IN CHILDREN AND YOUNG PEOPLE IN WESTERN AUSTRALIA

Hannah Moore, Tom Snelling, Claire Waddington, Christopher Blyth, Thomas Riley, Deborah Lehmann, Parveen Fathima

Enteric infections cause significant mortality and morbidity worldwide, in both resource rich and poor settings. In WA, enteric infection is one of the leading causes for infection-related hospitalisations in children under the age of 2 years and Aboriginal infants are 8 times more likely to be admitted for enteric infections than non-Aboriginal infants.

Although enteric infection is usually self-limiting in healthy children, it can lead to acute morbidity through dehydration and chronic morbidity through failure to thrive and under-nutrition. Furthermore, some enteric pathogens can translocate into the normally sterile bloodstream causing bloodstream infection (BSI) and sepsis.

The causative pathogens of enteric infection are geographically, seasonally and temporally variable. Rotavirus infection has been the single most important cause of enteric disease in WA as with elsewhere in Australia and globally, but bacterial enteric infection due to Campylobacter spp., Salmonella spp., Shigella spp. and parasites are also frequently reported in infants in the Northern Territory, and those aged less than 5 years in remote WA, especially in Aboriginal infants.

Rotavirus vaccination commenced in WA in mid-2007 and has been accompanied by a reduction in rotavirus-specific and all-cause gastroenteritis hospitalisations. We hypothesise that rotavirus immunisation has not only had a direct impact on rotavirus gastroenteritis, but it also has an indirect impact on non-rotavirus enteric pathogens by reducing their transmission. There are a number of observations arising from the field trial and post licensure experience with rotavirus vaccines which support this hypothesis and yet it has never been formally tested. These observations include the disproportionate impact of vaccination observed against severe diarrhoea and diarrhoea-related mortality. Because of its capacity to directly link hospitalisation with pathogen-specific pathology data, WA is in a unique position to address this hypothesis. The results are highly significant for understanding the overall impact of rotavirus vaccination, especially among Aboriginal children and in resource-poor settings where non-rotavirus pathogens account for a significant proportion of the total diarrhoeal disease burden.

Accurate data on causative pathogens for community-acquired enteric infection are needed to guide medical management and further public health interventions. Pathogen data relevant to WA are limited. WA is climatically diverse, and has a large remote Aboriginal population among whom enteric disease causing pathogens differ from those in the non-Aboriginal population. A recent study has shown diverging temporal trends in gastroenteritis hospitalisation rates in Aboriginal and non-Aboriginal children in the different geographical regions of WA. We need to study the changes, if any, in the prevailing enteric pathogens over time to determine if they are

driving these trends.

In this project, we propose to investigate the pathogen-specific burden of community-acquired enteric and bloodstream infection in Aboriginal and non-Aboriginal populations, focusing on children presenting to Emergency Department facilities or being hospitalised across the state of Western Australia. The results will allow us to evaluate the overall impact of WA's rotavirus vaccination program and will inform future preventive and management strategies.

Specific aims of this project are:

1. To characterise the epidemiology and pathogen- specific burden of disease for community-acquired enteric disease including enteric bloodstream infection among Western Australian (WA) children
2. To describe the changes over time in the prevalent enteric pathogens causing presentations for diarrhoea and blood stream infection (BSI), and to compare overall and pathogen-specific rates of infection pre and post rotavirus vaccine introduction, using non-enteric BSI (Staphylococcus, Pneumococcus and Group A Streptococcus) as a control outcome.
3. To determine the demographic and clinical risk factors for community-acquired infection with enteric pathogens in WA.
4. To assess the impact of co-morbidities on disease outcome measured by 30 day mortality and duration of hospitalisation.
5. To correlate location specific rates of enteric diseases with publicly available data on location specific vaccine coverage.
6. To determine the reduction in emergency presentations and hospitalisations attributable to the rotavirus vaccine program.
7. To characterise changes in antimicrobial susceptibility of enteric pathogens over time.
8. To prioritise future public health interventions to address the residual burden of enteric diseases in WA.

In 2013, the application for data custodian approvals was submitted to the Data Linkage Branch in WA.

Enteric (gut) infections are a major cause of illness in children and young adults. Aboriginal children suffer from more gut infections compared with non-Aboriginal children. In addition to dehydration, severe gut infections can give rise to bloodstream infections (BSI) and other nutrition/growth related health problems. By bringing together the birth, hospitalisation, and laboratory records of children across Western Australia over the last 10 years, we will investigate which pathogens (bacteria, viruses or parasites) are responsible for enteric infection related health care presentations in children, who are most at risk and what factors (such as age, region of residence, infant low birth weight, maternal age etc) predicts the severity of illness. We will assess the overall impact of the rotavirus vaccination program introduced for children in Western Australia in 2007. This will help us to better target further prevention and management strategies for these infections.

Funders of the project: Princess Margaret Hospital Foundation New Investigator Project Grant

INFECTIOUS DISEASES COMMUNITY REFERENCE GROUP

Deborah Lehmann, Hannah Moore, Kirsten Alpers, Glenn Pearson, Anne McKenzie

An Infectious Diseases Community Reference Group (CRG) has been meeting at the Institute four times a year since it was convened in 2007. The group is comprised of Aboriginal and non-Aboriginal community members, Institute researchers and representatives from the Western Australian Department of Health, the Vaccine Trials Group (VTG), the Meningitis Centre and the Institute's Consumer and Community Advisory Council. Community members provided input and advice to researchers who presented their proposed research studies to the group and identified areas of particular community concern. Presentations to the CRG are part of informing the wider community about infectious disease research conducted both within the Institute and externally. In 2013, presentations covered such diverse topics as refugee health, strategies to improve the rates of immunisation in WA, the effect of maternal vaccination during pregnancy on influenza in babies, diarrhoeal infections and the development of food allergy after whooping cough vaccination. The CRG continued with the process of reviewing and commenting on a list of plain language summaries of infectious disease research projects at the Institute and VTG, provided feedback on documents intended for study participants and assisted researchers by providing letters of support for specific projects.

GROUP A STREPTOCOCCAL DISEASE AND RHEUMATIC HEART DISEASE

Development of a long acting penicillin formulation

Jonathan Carapetis, Claire Waddington, Rosemary Wyber

The aim of this project is to prevent the suffering and unnecessary deaths caused by RHD by developing a long term, deliverable, affordable penicillin based treatment that will prevent recurrent Group A Streptococcal infection and ongoing heart damage in patients with acute rheumatic fever. Although this recurrent infection can be prevented by penicillin treatment, this currently requires painful monthly injections that are logistically difficult and expensive to provide. As a result most patients at risk of RHD do not receive adequate penicillin, and patients continue to suffer with, and die of, preventable heart disease. This project will develop a method of penicillin administration that last for at least a year, providing a practical, less painful method of treatment compared to monthly injection. Ultimately, this will vastly increase the number of patients successfully treated, thereby preventing RHD and ultimately decreasing mortality from this disease.

Funders of the project: NHMRC Project Grant #572590.

Genetic associations of rheumatic heart disease in Aboriginal Australian and Torres Strait Island communities

CIs Jonathan Carapetis, Jenefer Blackwell

Rheumatic heart disease is highly prevalent in Aboriginal people in Australia and leads to early cardiac disease. Despite decades of research, the underlying genetic mechanisms for why it occurs are not well understood. We are conducting a genetic study to better understand why some people are susceptible to RHD and others are not. The study will involve substantial Aboriginal leadership and consultation and will be a model for the conduct of genetic studies in Aboriginal populations.

Improving delivery of secondary prophylaxis for rheumatic heart disease

CI Jonathan Carapetis

Rheumatic heart disease is a major health problem in Indigenous communities. Continued progress in controlling RHD requires an understanding of how to improve delivery of regular injections of penicillin - secondary prophylaxis. We will evaluate a systems-based approach to improving delivery of SP, using a stepped-wedge trial in 12 communities in the Northern Territory and Queensland. If successful, this model will provide a practical and transferable model.

Tools for implementing rheumatic heart disease control programmes (TIPs)

Rosemary Wyber, Jonathan Carapetis

TIPs collates 60 years of program implementation experience from around the world to understand how comprehensive programmes to control rheumatic heart disease can be delivered. In conjunction with the World Heart Federation TIPs will be available to support the design and delivery of programmes in low and middle income countries

Intellectual Disability

WA CEREBRAL PALSY STUDIES

Eve Blair, Linda Watson, Fiona Stanley, Carol Bower

Cerebral palsy (CP) is an umbrella term covering chronic neurological conditions affecting movement and posture, ranging in severity from barely noticeable to severely disabling. The primary pathology lies in the brain, but for most the cause is poorly understood. CP results in life-long disability, and since there is as yet no cure, prevention and effective management are top priorities.

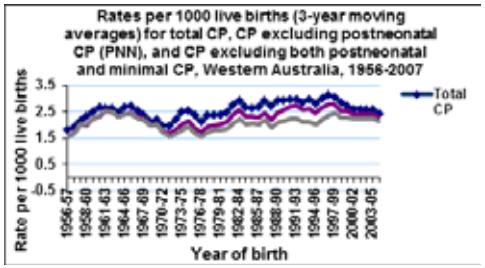
THE WA REGISTER OF DEVELOPMENTAL ANOMALIES - CEREBRAL PALSY

Linda Watson, Eve Blair, Fiona Stanley, Carol Bower

Statutory notification of CP and birth defects was introduced in WA in January 2011, with the CP and Birth Defects Registers combining under the name of the WA Register of Developmental Anomalies (WARDA). The WA CP Register is now known as WARDA – CP.

WARDA - CP, which has existed continuously since 1979, is used to monitor the occurrence of CP in WA, carry out research to investigate its causes and evaluate treatment strategies, identify CP as a long-term outcome in other WA studies and assist in the planning of services for people with CP. A birth cohort is included in analyses after case data are updated at age 5 years; the register is now considered complete to 2007.

WARDA - CP is also responsible for contributing data to the Australian CP Register (ACPR), a national collaboration initiated by the WA team in 2002 to provide information about CP throughout Australia and create a larger study population to enable more effective research, particularly into the less frequently occurring types of this very heterogeneous condition. The administrative centre relocated in 2007 to the Research Institute of the CP Alliance in NSW where it continues to flourish. The first report of the ACPR was published in 2009, and the second published 2013 considers birth years 1993-2006. Both are available at http://cpregister.com.



Funders of the project: WARDA - CP is presently funded by NHMRC Program Grant #572742 Early developmental pathways linking health, disability, education, welfare and justice (2010-2014).

DEVELOPING A RELIABLE SYSTEM OF DESCRIBING CP

Sarah Love, Noula Gibson, Eve Blair, Linda Watson

The cerebral palsies include a wide range of motor impairments across the spectrum of severities and may be accompanied by a wide variety of other impairments which can greatly affect both functionality and treatment options. The validity of generalising the results of CP research depends heavily on a consensus understanding of what segment of the CP population the research refers to. International attention has been focused on the challenge of standardising the classification of CP for several decades, during which time WA has been at the forefront of promoting description rather than classification and developing a reliable system of describing the clinical features of CP. We are continuing to develop and promote an innovative diagrammatic limb-by-limb CP Description Form which incorporates the Australian Spasticity Assessment Scale (ASAS) devised by Sarah Love and Noula Gibson, two Cerebral Palsy Habilitation Physiotherapists. A booklet defining every aspect of the CP Description Form and a Training and Reference video demonstrating the use of the ASAS and showing examples of the different forms of CP are both ready for publication and dissemination.

Funders of the project: PLAN Australia generously funded the development of the ASAS, the CP Description Form and the Training and Reference DVD. A PMH Foundation Special Project Grant 2007 has covered travel to conduct training sessions throughout WA, and an Innovative Research Grant from the CP Institute has funded the extension of training across Australia.

CASE CONTROL STUDIES OF CP IN TERM AND PRETERM INFANTS IN WA, 1980 TO 1995

Eve Blair, Sarah McIntyre, Linda Watson, Nadia Badawi, Karin Nelson

Comprehensive maternal, birth and neonatal information on all CP cases, matched controls, and a representative sample of unexplained perinatal deaths born 1980-1995 was collected from birth hospitals throughout the State. This has provided a wealth of data from which to identify causal pathways to the different outcomes. The primary aim of these studies is to prevent the occurrence of brain damage responsible for CP by identifying points on each causal pathway to CP at which it may most effectively, efficiently and ethically be interrupted. Data analysis continues with the intent to explore causal pathways and report research findings at local, national and international forums.

The current focus of our analyses is on singleton births occurring after 35 completed weeks of gestation (term and late preterm singletons). This relatively low risk group has received little research attention, yet it comprises 30% of all perinatal deaths and 70% of all CP and is very likely to be the most aetiologically heterogeneous. In an effort to create more aetiologically homogeneous groups we have identified subjects with abnormal neonatal neurological signs and the subset of this group whose signs were attributed to acute intrapartum hypoxia. We have identified that 53% of neonatal deaths and 68% of CP in our sample did not appear neurologically abnormal in the neonatal period. The antecedent factors of all outcomes are being compared.

The original data collected information on birth defects identified in the neonatal period. Linkage with WARDA-birth defects has now provided data on all birth defects identified up to the age of 6 years, greatly increasing the proportion of CP cases with an identified birth defect and demonstrating that it is the most frequently identified risk factor for CP in term and near term births, particularly if accompanied by fetal growth restriction.

Funders of the project: This case-control study was funded by NHMRC Program Grants #353514 (2005-2009) and #572742 (2010-2014). An Innovative Research Grant from the CP Institute provides additional funds for analysis and travel.

PUBLICATIONS 2013

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IDEA - INTELLECTUAL DISABILITY EXPLORING ANSWERS

Helen Leonard, Jenny Bourke, Ami Bebbington, Patrick Fitzgerald, Amanda Langridge, Geoff Hammond, Deirdre Croft, Carol Bower

The IDEA Database provides an infrastructure for population-based epidemiological research into the causes and prevention of intellectual disability as well as the outcomes for those affected. Information in the database is sourced from data from the Disability Services Commission (DSC) since 1953, as well as information from the Department of Education for children born since 1983. IDEA has been updated with notifications of children identified with an intellectual disability from the Department of Education and the Disability Services Commission to the end of 2010. These records are linked by the Western Australian Data Linkage Unit (DLU) to each other and to all current notifications on the database in order to minimise any duplications. Medical information on cause of intellectual disability is provided from Disability Services Commission.

The current prevalence for intellectual disability calculated on the WA births from 1983-2003 and ascertained up to 2010 is estimated to be 17.4/1000 live births. This is an increase on the earlier prevalence estimate of 14.3/1000 live births, calculated using births from 1983-1992 and ascertained up to 1999. These data suggest that the prevalence of mild-moderate intellectual disability may have increased among children born in the nineties. This will be further investigated to try to identify the reason for this rise and whether it might relate to an increase in the diagnosis of autism spectrum disorders or another cause.

Recent articles published in the scientific literature using data from the IDEA database have investigated hospitalisations in children with intellectual disability and autism, and shown an increased risk of hospitalisation in childhood which varied from 2 to 10 times that of the rest of the population. A further study investigated the pattern of hospitalisations for children with Down syndrome and found respiratory and ear infections were the most common reasons for admission. These important findings can inform service planning and resource allocation for these children with special needs. A book chapter, which outlined the value of linked data for intellectual disability

research, was published in the International Review of Research in Developmental Disabilities. A report on the IDEA Database over the last 10 years has also been drafted and will be published early in 2014.

Investigations currently underway include: the causes of hospitalisation for children with intellectual disability and autism; exploring the pathways to contact with Juvenile Justice for Aboriginal children in order to support a strategy for change; the relationship between a woman's psychiatric history and the likelihood of her subsequent offspring developing intellectual disability or autism; and the co-occurrence of intellectual disability, cerebral palsy and birth defects.

The IDEA Database is overseen by the IDEA Advisory Council. The 2013 membership included Professor Carol Bower (Chair), Dr Helen Leonard, Jenny Bourke, (TICHR), Dr Vera Morgan (UWA), Richard Sanders (Department of Education), Nick Cantatore (DSC), Dr Peter Rowe (State Child Development Centre) and Charlie Rook (Consumer, who sadly passed away December, 2013).

Funders of the project: Disability Services Commission.

THE TRANSITION FROM SECONDARY SCHOOL TO ADULTHOOD: EXPERIENCES AND LIFE OUTCOMES FOR YOUTH WITH AN INTELLECTUAL DISABILITY AND THEIR FAMILIES

Helen Leonard, Carol Bower, Nick de Klerk, Gwynnyth Llewellyn, Stewart Einfeld, Trevor Parmenter, Vivienne Riches, Bruce Tonge, Nick Lennox, Ron Chalmers, John Brigg, Greg Lewis, Jackie Softly, Jenny Bourke, Paula Dyke, Kitty Foley, Katherine Bathgate, Terri Pikora, Sonya Girdler, Lyn McPherson.

This ARC Linkage project, which developed from an ARACY Seed-funding grant, seeks to explore the challenges faced and outcomes achieved by young people with an intellectual disability as they move from secondary school into adult life. There are likely to be major life changes for these young people as they move into adulthood with respect to work, where they live, who cares for them, how their health and therapy needs are managed and how they spend their days. The study is investigating the factors at an individual, educational, family, and societal level which contribute positively and negatively to a 'good' outcome for the young person and their family.

This study involves young people with intellectual disability aged 16 years and over from four separate sources: i) Down syndrome NOW cohort in WA, (ii) the Queensland Centre for Intellectual and Developmental Disability's ASK study (a five year project aiming to improve the health of young people with intellectual disability); (iii) the Australian Child to Adult Development (ACAD) Study at the University of Sydney and (iv) the Australia-wide Rett syndrome cohort. We used the World Health Organization's International Classification of Functioning, Disability and Health (ICF) framework to take into account the many issues which may affect a person's participation in all aspects of life.

In 2009/10 questionnaires were administered to 269 families of young people with Down syndrome in Western Australia. Of the 203 (75.0%) returned, 164 (80.8%) had left school with ages varying from pre-transition (16-17 years), early transition (18-20 years) to late transition (23-31 years). Follow-up questionnaires were administered in 2011/2012 to 229 families with 197(86%) families responding.

In consultation with the WA research team the Queensland group administered a similar questionnaire to the parents of the young people, aged between 17 and 23 years, in the Queensland ASK cohort, with 150 (59%) respondents. We are currently comparing the transition experiences of the young people and their families in the WA and Queensland cohorts. Using the existing ACAD data previously collected in New South Wales and Victoria we are comparing the behavior of individuals with Down syndrome using both the WA and ACAD cohorts, with young people with intellectual disability of other cause in the ACAD cohort.

Based on the 2009 Down Syndrome NOW data, among those who had left school (n=164) the most common main day occupation was sheltered employment (39.0%), followed by open employment (25.6%) and alternatives to employment (ATE) (25.0%) while the remainder (10.4%) attended training. Not unexpectedly young adults who were reported as functioning better within self-care, community and communication skills were more likely to be participating in open employment or training than those in sheltered employment or alternatives to employment. However we did not find any evidence that poor health status adversely impacted on workplace participation. Similarly, families of young people with Down syndrome attending open employment reported better quality of life than families of young people attending sheltered employment. The young person's behaviour had a weak association with family quality of life.

Using the data from three time-points in 2004, 2009 and 2011 we looked at the trajectory of behavior in young people by age. We found that whilst the disruptive, self-absorbed, communication disturbance and anxiety components of behavior improved with age, the social-relating problems and depressive symptoms persisted. These findings contribute to the understanding of mental health status across the developmental time periods in people with Down syndrome. We also examined the changes in behavior over time for young people according to their day occupation. We found that participation in open employment was associated with an improvement in behaviour from 2009 to 2011 compared to those in other day occupations.

The social participation of young adults with Down syndrome from a parental perspective and its relationship with the physical and social environment was explored. Young people were found to have more difficulty participating in social roles (e.g. relationships, community life, recreation etc.) than they did participating in daily activities (e.g. personal care, communication, housing etc.). The most commonly reported barriers to participation were negative attitudes of strangers, and lack of support from friends, availability of jobs and public transport.

We also conducted a qualitative study to investigate the experiences of mothers of

young adults with either Down syndrome or Rett syndrome who were transitioning from secondary school to adult life. In contrast with Rett syndrome, mothers of young adults with Down syndrome described more difficult pathways to attaining stability in adult roles. The facilitators and barriers which emerged were in the area of support, relationships, services, systems and policies. The study highlighted the unwavering commitment of parents to their son or daughter with an intellectual disability and the extraordinary resourcefulness of many families in their quest to ensure that their son's or daughter's quality of life is maximised.

INTERNATIONAL RETT SYNDROME STUDY: INTERRETT

Helen Leonard, Alison Anderson, Ami Bebbington, Nada Murphy, Jenny Downs, Heidi Meyer, Nan Hu.

Rett syndrome is a rare neurological disorder which has an incidence of diagnosis of 1:9000 by the age of 32 years and is associated with mutations in the MECP2 gene. Given the low number of cases at a national level (~415 in Australia) international collaboration and data collection are imperative. The InterRett database project allows clinicians and families caring for an individual with Rett syndrome to directly contribute to the global research effort by completing web or paper-based questionnaires. The project, which is funded by the International Rett Syndrome Foundation, was established in 2002 and continues to grow and expand with online questionnaires available in Mandarin and six European languages. The database currently contains ~ 2,750 cases representing over 50 different countries. New participants register using a form on the project website (also available in different languages). International support for the InterRett project continues to strengthen, particularly in China and we have a Chinese national, Nan Hu who is providing translational expertise and assisting families in submitting their information. The website also allows users to: generate graphs based on summary data; download clinical guidelines for the management of scoliosis and gastrointestinal issues; and to read snapshots of the over 20 peer-reviewed publications arising from analyses of the InterRett data. Our research covers a wide range of topics such as: pain sensitivity; the characteristics that influence diagnosis; diagnostic challenges in China; the influence of mutation type or DNA variations in the BDNF gene on clinical severity; and ageing and survival in Rett syndrome. To allow families to contribute at all levels of the research process, from study design to the dissemination of findings, a Consumer Reference Group (CRG) has been established. In 2013, CRG representatives from the US, UK and Australia successfully provided their input during two teleconferences. This highly successful framework for the collection of data for a rare disorder on a global scale has been replicated for the rare CDKL5 disorder and is now being developed for MECP2 duplication syndrome.

TOWARDS EVIDENCE BASED CARE FOR RETT SYNDROME: A RESEARCH MODEL TO INFORM MANAGEMENT OF RARE DISORDERS

Helen Leonard, John Christodoulou, Carolyn Ellaway, Helen Woodhead, Jenny Downs, Elizabeth Geelhoed, Elizabeth Elliott, Peter Jacoby, Ian Torode, Gordon Baikie, Mark Davis, Bruce McPhee, Madhur Ravikumara, Sue Thompson, Margaret Thomson, Ami Bebbington, Amanda Jefferson, Sonya Girdler, Anna Urbanowicz, Kingsley Wong, Catherine Bunting, Caitlin Marr, Orla McIlroy, Geoff Askin, Maree Izatt

Rett syndrome is a rare neurological disorder usually affecting females and caused by a mutation in the MECP2 gene. AussieRett, as the Australian Rett Syndrome Study is known, is a population-based study which, since 1992, has followed 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.

We are currently in the final year of an NHMRC funded study commenced to facilitate best practice in clinical decision making, laboratory procedures and counseling in relation to the diagnosis and management of Rett syndrome. This study aims to:

- develop recommendations for the diagnosis process for Rett syndrome;
- identify longitudinal changes in gross motor abilities, hand function and development of scoliosis and;
- evaluate the clinical effectiveness of scoliosis and gastrostomy surgery in children and adults with Rett syndrome.

For the diagnostic study questionnaires relating to the characteristics of their patients have been completed by 134/141 clinicians who requested MECP2 testing from one of the three Australian accredited laboratories for 225 patients. These are completed prior to the result of genetic testing being known. The goal is to develop tools to support clinical decision making to facilitate timely diagnostic testing for girls with Rett syndrome, thereby assisting families in the often stressful early stage when seeking a diagnosis. Data collection has been continuing since July 2011 and will continue through 2014.

As part of the longitudinal study follow-up questionnaires were administered in September 2011 to 269 families enrolled in the study and families could return data online, on paper or during a telephone interview. The response fraction from parents and care-workers has been excellent at over 86% and we are also receiving some additional family data. Information has been collected on the affected individual's functional ability in daily living, behaviour, hand function, medical conditions, use of health and education services, and family health and functioning. Questions have also been included to assess parental satisfaction with spinal fusion and gastrostomy procedures for those children and adults who have undergone these procedures.

Scoliosis is a common complication of Rett syndrome, however little is known about the natural history of curve progression and the relationship with the type of genetic mutation, age and mobility level. X-ray data on the progression of the spinal curve of children and adults with scoliosis has been collected on 195 girls and women with scoliosis and there will be some additional data collection

throughout 2014. Spinal fusion (for scoliosis) and gastrostomy insertion (feeding tube into the stomach due to problems with swallowing or poor growth) are surgeries faced by many children and adults with Rett syndrome. The decision to proceed with these surgeries is often difficult for families, and both clinicians and families need accurate information about the short and long term risks and benefits of these procedures. Currently, there are gaps in our knowledge of outcomes. Collection of data from the hospital records is near completion and will supplement the questionnaire data. We are also collecting video data and by year end 2013 135 families had already provided video footage of their daughter's functional abilities. Video data collection will also continue through 2014.

The AussieRett study has continued to involve consumers through the Consumer Reference Group, biannual newsletters and online via the new website and Facebook page. The Consumer Reference Group, involving family members from across Australia via regular teleconferences, is an opportunity to discuss and give valued feedback on all facets of the study.

The study has a multi-disciplinary investigative team from the fields of medicine, physiotherapy, epidemiology, biostatistics, dietetics and occupational therapy. It has national collaborations with the Children's Hospital at Westmead and the Children's Hospital Randwick, Sydney, the Royal Children's Hospital, Melbourne, the Mater Children's Hospital, Brisbane and the Royal Children's Hospital, Brisbane. We will shortly have collaborations with clinicians at the Women's and Children's Hospital, Adelaide and the Monash Hospital, Melbourne.

During 2013 fourteen articles relating to Rett syndrome were published or accepted for publication by our group. These articles included investigations of epilepsy, poor growth, gastrointestinal dysmotility, gallbladder disease and the regression period in Rett syndrome. We have also investigated participation in activities in the community and have written a review on hand function in Rett syndrome. Another study recruited families with a daughter with Rett syndrome in China and examined caring during everyday life.

Funders of the project:

Current: NHMRC Project Grant (1004384), NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

DEVELOPING CLINICAL GUIDELINES FOR THE MANAGEMENT OF GASTRO-INTESTINAL DISORDERS AND BONE HEALTH IN PATIENTS WITH RETT SYNDROME

Jenny Downs, Helen Leonard, Gordon Baikie, Madhur Ravikumara, Nusrat Naseem, Deirdre Croft, Amanda Jefferson, Helen Woodhead, Sue Fyfe, Aris Siafarikas

Rett syndrome is frequently associated with poor growth, feeding difficulties and problems with gastro-oesophageal dysmotily such as reflux, constipation and abdominal bloating. There is limited literature on management strategies for these common gastro-intestinal conditions in Rett syndrome and we have previously used the Delphi technique to develop a consensus for items that describe their assessment and management. Our set of recommendations for the assessment and treatment of gastro-intestinal issues has been the subject of three publications on the topics of poor growth, dysmotility and gall bladder disease in Rett syndrome. We have also produced a lay booklet that presents the guidelines in a format suitable for families together with two leaflets for clinicians on the topics of poor growth and dysmotility. These have been disseminated to all families with a daughter with Rett syndrome in Australia, is available on our Telethon Kids Institute website, and has been additionally disseminated by family associations in the US and UK.

Rett syndrome is also associated with osteoporosis and a greater likelihood of fracture in comparison with the general population. We recruited a panel of 35 expert clinicians and researchers and again used the Delphi technique to develop guidelines for optimal bone health in Rett syndrome. A manuscript describing this research is in preparation and we envisage writing a lay booklet and clinician leaflet for dissemination of findings as we did for the gastrointestinal guidelines.

Funder of the project: Rett Syndrome Association UK.

THE NATURAL HISTORY OF THE CDKL5 DISORDER: DEVELOPMENT OF AN INTERNATIONAL REGISTER

Stephanie Fehr, Helen Leonard, John Christodoulou, David Forbes, Simon Williams and Jenny Downs

The CDKL5 disorder is caused by mutations on the cyclin-dependent kinase-like 5 (CDKL5) gene. Clinical features include early-onset seizures (generally within the first three months of life), global developmental delay, abnormal muscle tone, hand stereotypies, gastrointestinal problems and bruxism. In the past this disorder was considered an atypical form of Rett syndrome, however our research published in 2012 and other articles published since conclude that it is an independent disorder.

Since our 2012 publication, which included the largest cohort of individuals with the CDKL5 disorder, we worked on developing an International database for the CDKL5 disorder. This was done in collaboration with the International Foundation for CDKL5 Research. Data collection commenced in September 2012 and involved families of individuals with the CDKL5 disorder completing a questionnaire either online or on paper. The questionnaire has also been translated into French, German and Spanish. By year end 194 families had been recruited and 77 had already completed the questionnaire with a further 50 in progress. In October 2013 we presented some initial preliminary findings at the 3rd European Rett syndrome Conference in Maastricht. We investigated the functional abilities of individuals with the CDKL5 disorder, the occurrence and impact of gastrointestinal problems and the treatment and pattern of epilepsy. These findings were also included in our first International CDKL5 disorder database newsletter sent to all participating families and clinicians. Data collection will continue in 2014 and we plan on presenting our findings at the 2nd International CDKL5 Research Symposium and Family Conference in Washington in June 2014.

Funders of the project: Nil

DOWN SYNDROME CLINICAL TRIAL- BTD-001

Helen Leonard, Jenny Downs, Jenny Bourke, Peter Richmond, Jasminka Murdzoska, Kingsley Wong, Tanya Stoney, Gabi Willis, Barbara Anderson

The purpose of the study is to determine if a new formulation of the drug called BTD-001, which behaves as a GABA antagonist, can improve function and cognition in people with Down syndrome. This randomized, double blind, placebo-controlled trial is assessing the safety and preliminary efficacy of the drug. The study involves taking an oral formulation of BTD-001 for 12 weeks and undergoing cognitive tests over 7 clinic visits. Participants are monitored for adverse events for the duration of the study.

The study is being conducted in eight sites across Australia. For our site study participants have generally been contacted through the Down Syndrome NOW database developed at the Institute through previous survey studies involving families with a child with Down syndrome. Participants must be aged 13-35 years, be able to complete the required cognitive tests and be screened for current medical conditions such as epilepsy and hypothyroidism, which may indicate exclusion from the study. Currently thirteen individuals have been screened and eight have been randomized.

MULTI-REGISTRY ANALYSES OF RISK FACTORS FOR AUTISM: ICARE AND MINERVA

chaeline Bresnahan, Kim Carter, Jakob Christensen, Lyn Colvin, Richard Francis, Mika Gissler, Emma Glasson, Therese Grønborg, Raz Gross, Nina Gunnes, Geoff Hammond, Mady Hornig, Christina Hultman, Amanda Langridge, Marlene Lauritsen, Helen Leonard, Erik Parner, Abraham Reichenberg, Sven Sandin, Andre Sourander, Camilla Stoltenberg, Auli Suominen, Pa l Sure´n, Ezra Susser

Although it is well known that genetics are important in the aetiology of autism, the recent increase in the prevalence of autism as well as reports from some studies of a lower familial contribution suggest that non-genetic and environmental factors may also be important. For other diseases with complex causes, like diabetes or cancer, it has been necessary to pool data across many different study groups and populations to achieve large enough sample sizes. The International Collaboration for Autism Registry Epidemiology (iCARE) was established as a multinational consortium for sharing and pooling of data for research on autism spectrum disorders (ASDs). iCARE partners from seven different countries (Australia, Denmark, Finland, Israel, Norway, Sweden, and the USA) contribute data for analyses. The data that are used in iCARE come from data sets that already exist in each country for public health purposes. These public health data sets have information on everyone in the country or the state, such as data sets that record every birth or death. The data in iCARE from all seven partners are best used for studies that require very large sample sizes or for making comparison across the different countries. The purpose of the original project funded by Autism Speaks was to establish the iCARE partnership and build the necessary tools and ways to carry out research on data from different countries. Another purpose was to undertake studies on risk factors and trends in autism using the pooled data.

Data from each site undergo rigorous harmonization and quality control processes prior to analyses; local datasets are fixed snapshots of registry data at a particular point of time and the harmonization process is repeated following registry data updates (new ‘‘snapshots’’), the addition of new variables, or variable modifications. Analyses are performed using database federation techniques developed and maintained by our Institute’s bioinformatics group. These techniques permit transparent access to iCARE datasets located and managed at each site without the need for data export for pooling or permanent archiving at a single location. Thus iCARE has created a computational infrastructure with a secure, web-based, interface to facilitate analysis of the federated, harmonized, research datasets. Investigators give careful consideration to the consequences of site differences in case ascertainment (e.g., registry-specific variation in ascertainment of different ASD diagnostic or phenotypic subtypes), differences in registry reporting, and changes in diagnostic criteria across sites and over time, and their impact on case characteristics and associations with risk factors. Pre-analytical, descriptive steps to assess between site heterogeneity include exploration, variable by variable, of autism and risk factor differences over time, by site, and diagnostic system. Overall, the benefits of establishing iCARE include: (1) cost efficiency through use of existing data resources; (2) flexible infrastructure accommodating current research needs and future network growth and data upgrades; (3) flexibility in study designs to suit particular analyses (e.g., cohort, case-cohort, multigenerational or sibling designs); (4) largest sample sizes achieved to date based on federated data that enhance statistical precision; (5) ability to characterize population trends in reported diagnoses over time (e.g., by age at reporting, birth cohort or time period), as well as changes over the life course of affected individuals; and (6) enhanced comparison and interpretation of between-site results based on data harmonization and application of uniform analytic methods to multi-site data.

In 2013 a paper describing the iCARE infrastructure and methodology was published whilst work was concurrently being undertaken on a number of analyses including, for example, investigations of the relationships between parental age and seasonality of birth with autism. The previous year the iCARE researchers under the leadership of Dr Abraham Reichenberg from the Mount Sinai School of Medicine had been successful in their application to be a NIH Autism Center of Excellence. The goals of the new program known as MINERvA are to examine: fundamental controversies concerning familial and environmental contributions to risk for ASD; transmission of risk across generations; pregnancy-related environmental factors in ASD, and the potential role of epigenetic changes in those factors. Building on the existing iCARE network study data will now be based on over 4.5 million births (1998-2007), over 20,000 cases of ASD, and family linkages over three generations and will be again analysed using database federation via a computational infrastructure with a secure, web-based, interface.

Funders of the project: Autism Speaks (iCARE), National Institute of Health (MINERvA).

DETERMINANTS AND OUTCOMES OF PRETERM BIRTH & PATHWAYS INTO DEVELOPMENTAL DISORDERS

Fiona Stanley, Helen Leonard, Geoff Hammond, Amanda Langridge, Kristjana Einarsdottir, Ami Bebbington, Jenny Bourke, Nick De Klerk, Peter Jacoby, Steve Ball, Gavin Pereira, Eve Blair

Increases in preterm birth and survival over time of those born pre-term are occurring due to a range of factors. These include increasing maternal age and co-morbidity (particularly obesity and maternal diabetes), increases in multiple births, social factors such as higher fertility rates in socially disadvantaged high risk mothers and changes in obstetric practice relating to reproductive technologies, early induction of labour and use of caesarean section. Our group undertakes complex statistical analyses principally using linked deidentified Western Australian population data relating to pregnancies, births and hospitalisations to investigate the determinants and outcomes of preterm birth and the pathways leading to developmental disorders. We have already shown how the determinants of both spontaneous and medically indicated pre-term births are changing over calendar time. We have also compared neonatal outcomes for babies born pre-term in the public and private systems. Interestingly following the Australian Private Health Insurance Incentive policy reforms, which were implemented in 1997–2000, births in privately insured patients and also caesarean deliveries increased. We also showed that from 1996 to 2005, the rising caesarean delivery rate in nulliparous women could mostly be attributed to an increase in prelabour caesarean deliveries for private patients delivering in private hospitals. Our current work also includes investigations of the relationship between various environmental and geographic factors and pregnancy complications and birth outcomes.

Further to our examination of the causes of pre-term birth, the next step will be to follow these vulnerable infants born at different gestational ages and determine what factors increase or decrease their likelihood of survival with or without a major developmental disability (e.g. intellectual disability, cerebral palsy and autism). This will allow us to explore the impact of changes in antenatal and perinatal care on these important pathways. As well as measuring the contribution of preterm birth to developmental disabilities, we also plan to measure the later hospitalisation experience of children born at different gestational ages and with different developmental disabilities. This will provide the basis for economic analyses of the costs associated with preterm birth and with specific developmental disabilities.

Funders of the project: NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

Looking at Language

LOOKING at Language is the first and only study to follow WA children from the start of language at 2 years to 14 years when children are expected to have sophisticated language and to read well. Our focus on the early years is critical to identifying children who need help and knowing how to treat their language difficulties and prevent reading difficulties later on.

Looking at Language: Professor Mabel Rice from the University of Kansas, Professor Cate Taylor and Winthrop Professor Stephen Zubrick from the Telethon Kids Institute and Professor Shelley Smith from the University of Nebraska Medical Center.

Our uniquely human capacity for language is one of the most important development accomplishments of childhood. The critical role of oral language in enabling literacy, education and employment means that to study language acquisition is to study a major pathway for human development. We cannot underestimate the value of communication and the value of language. It transcends a child's emotional and mental development. It affects their education, their social standing and their ability to relate in all circumstances and at all levels. Looking at Language places the institute at the forefront of research in language and literacy worldwide. Our approach and our research crosses a multitude of disciplines and sits within a number of the institute's Research Focus Areas The study, combines epidemiological, behaviour genetics and molecular genetics methods to study language development, language impairment, reading and reading impairment from infancy to adolescence.

This internationally unique study is following the language development of more than 2000 WA children from 2-14 years. It is the world's only study to conduct such detailed assessment of language and literacy development from infancy through the formative adolescent years. For the institute, the ability to continue following the study children through early adolescence is ground-breaking. It is vitally important that we understand the developmental course of language and literacy from infancy and what different trajectories mean for young people's opportunities at school and beyond. Data collection for this project is based entirely in WA and involves 5000 participants.

Ask any mum or dad what they consider a key milestone in their child's development and more often than not they will say it is language development. Looking at Language is following the language development of more than 2000 WA children from 2 – 14 years. It is the world's only study to conduct such detailed assessment of language and literacy development from infancy through the formative adolescent years. Our findings will help improve services and supports for children with language difficulties.

Funders of the project: NIH

The Western Australian Pregnancy Cohort (Raine) Study

The Raine Study is one of the largest successful prospective cohorts of pregnancy, childhood, adolescence and now young adulthood in the world and a unique resource for local, national and international researchers. 80% of the original participants are still active and committed to the project. Each member of the cohort has over 85,000 measures of health and disease and information on more than 2.5 million genetic variants. The Raine Study began in 1989 at King Edward Memorial Hospital with

the recruitment of 2900 pregnant women in early pregnancy in a research project assessing ultrasound examination. These families were followed through pregnancy and 2868 children born to the mothers were recruited into the Raine cohort. Since birth, the cohort participants been reviewed in detail on eleven occasions at ages 1, 2, 3, 5, 8, 10, 14, 17, 18, 20 and now at 23 years of age.

The Raine Study is governed by the Raine Study Executive Committee and managed by the Scientific Directors and Raine Study Manager. There are 25 collaborative expert groups under the leadership of a Principal Investigator, which include Anaesthesia, Asthma & Allergy, Cardiovascular & Metabolic, Cognitive Neuroscience, Dental Health, Developmental Origins of Health and Disease, Eating Disorders, Endocrinology, Epigenetics, Gastrointestinal & Heptology, Genetic Epidemiology, Growth, Hypothalamic-Pituitary-Axis, Infectious Disease, Language Development, Mental Health, Musculoskeletal, Nutrition, Ophthalmology, Otolaryngology, Physical Activity, Pregnancy & Birth, Reproductive Health, Risk Taking Behaviour and Sleep.

2013 was a busy and productive year for Raine Study management, the Raine Study Team, researchers and cohort participants. The 23 year old cohort assessment is in the final few months of data collection. A total of 54 research papers were published in peer reviewed journals in 2013.

The sixth Raine Study Annual Scientific Meeting was held on Friday 2 August 2013 at the UWA Club. The Event was opened by His Excellency the Governor and Mrs McCusker. Over 100 Raine Study Researchers attended the meeting and participated in over 20 presentations. The Raine Medical Research Foundation kindly donated prizes for the Best Presentations by a young researcher. These were awarded to Jessica Tearne and Gina Trapp.

The Raine Study Core Management provide top up PhD scholarships for Raine Study PhD students. In 2013 top-up scholarships were awarded to PhD candidates Elisha White, Carly Herbison and Seyhan Yazar.

THE RAINE STUDY 23 YEAR OLD FOLLOW UP - THE EVOLUTION OF CHILDHOOD OBESITY AND ITS RELATIONSHIP TO ADULT SLEEP DISORDERED BREATHING

Prof Peter Eastwood, Prof David Hillman, Dr Anne Smith, Dr Nigel Mcardle, Assoc Prof Rae Chi Huang, Stuart MacGregor, Jenny Mountain, Diane Wood, Raine Study Team, Raine Sleep Technology Team.

A major focus of the 23 year Raine Study assessment is sleep. Sleep affects all aspects of physical and mental well-being but almost nothing is known about the characteristics of sleep in young adults. The follow up of the Raine cohort at 23 years of age started in March 2012 and is planned to finish in June 2014. Participants are invited to spend the night in the Centre for Sleep Science (CSS) at the University of Western Australia and have a polysomnograph (Sleep Study). This study will utilise the longitudinal data collected on children and their families to determine, for the first time, the prevalence, clinical picture and risk factors for obstructive sleep apnea (OSA) and other sleep disorders in early adulthood. The specific aims of the study are to determine the prevalence of OSA syndrome in early adulthood; to characterise and establish the risk factors for OSA in young adults and identify early life predictors (including developmental, social, environmental and biological characteristics) associated with the development of OSA in young adults.

The participants also undergo other physical measurements and complete questionnaires. At the end of 2013 over 800 Raine Study Participants had completed a sleep study. This has been an amazing achievement involving sleep technologists, Raine Study staff, students, respiratory physiologists and other expert researchers.

Funders of the project: NH&MRC 1027449, Raine Study Core Management Funding

THE RAINE STUDY 23 YEAR OLD FOLLOW UP - TRANSITION FROM CHILDHOOD TO ADULT ASTHMA: PREDICTING PERSISTENT AND ADULT-ONSET ASTHMA IN YOUNG ADULTS IN THE RAINE LONGITUDINAL BIRTH COHORT.

Prof Graham Hall, Prof Pat Holt, Dr Elysia Hollams, Prof Zoltan Hantos, Prof Peter Sly, Prof Alan James, Prof Craig Pennell, Elisha White, Jenny Mountain, Diane Wood, Raine Study Team

The causes and development of asthma and related diseases is a key research program within the Raine Study. The Raine Study is one of the largest studies measuring lung function and bronchial responsiveness in preschool aged children. Major respiratory assessments were undertaken at birth, 6 and 14 years of age and findings led to early intervention trials targeting risk factors with the aim of preventing the development of asthma during childhood. The transition between the child and adult forms of asthma is a crucial research issue and doing a comprehensive respiratory assessment in the Raine Study cohort at age 23 provides a unique opportunity to track asthma status and development over 23 years. The primary objective of this project is to characterise the asthma-related clinical characteristics and associated immunophenotypes that persist beyond adolescence into early adulthood and to establish a baseline for the continuing study of chronic respiratory diseases in later life.

During the 23 year assessment, participants have a lung function test and an allergy skin prick test before settling into bed to be set up for the sleep study. In the morning, they have an assessment of airway hyper-responsiveness and further lung function testing. At the end of 2013 over 400 Raine Study participants completed the respiratory assessment.

Funders of the project: NH&MRC 1021858, Raine Study Core Management Funding

THE RAINE STUDY 23 YEAR OLD FOLLOW UP - A LIFE COURSE APPROACH TO CHARACTERISING AND PREDICTING INACTIVITY AND SEDENTARY BEHAVIOUR OF YOUNG ADULTS INCLUDING RELATED WORKLOSS

Professor Leon Straker, Dr Anne Smith, Rob Waller, Annegret Harries, Rebecca Nguyen, Raine

Study Team

Sedentary behaviour has been shown to be an independent risk factor for obesity, diabetes, cardiovascular disease and some cancers. Raine Study participants are fitted with ActiGraph accelerometers which are used to record all light, moderate and vigorous physical activity, sleep activity and sedentary behaviour. The accelerometers are worn continuously on the left wrist and right hip on the night of their sleep study and for the next 7 days and participants keep a brief log documenting their activity.

Quantitative Sensory Testing is measured by assessing the pressure pain threshold and the cold pain threshold. This is the first time that QST is being assessed a young adult cohort and these measures will be used assessing risk of chronic pain for when assessing work productivity and work loss.

Work loss due to work absenteeism or presenteeism (where a person is at work but not fully functional through illness or tiredness) creates a substantial burden on society. Health is an important reason for absenteeism and presenteeism. Work loss is being assessed using the World Health Organisation measures and is being done through the use of web based technology and smart phones.

Funders of the project: NH&MRC 1044840, Safe Work Australia, Raine Study Core Management Funding

Raine Study: Mental Health

INVESTIGATING THE INFLUENCE OF PRENATAL EXPOSURES AND THE POSTNATAL ENVIRONMENT ON CHILD AND ADOLESCENT MENTAL HEALTH TRAJECTORIES

Karina Allen, Monique Robinson, Andrew Whitehouse, David Lawrence

Early life (prenatal and birth to 5 years) factors are recognized as key contributors to mental health problems in later childhood and adolescence. This 1-year project commenced in May 2013 and seeks to determine the extent to which (i) prenatal exposures influence mental health problem trajectories from childhood through to adolescence, and (ii) preschool family and social factors can increase or decrease the effects of prenatal exposures on later mental health.

The results of the research are expected to help improve mental health prevention and early intervention initiatives, by identifying characteristics of the preschool family and social environment that may reduce mental health problems in children who experienced a high-risk prenatal environment.

To date, two manuscripts have been submitted for journal review and an additional two manuscripts are in preparation. Key findings from the submitted manuscripts include:

- The strongest prenatal predictors of child mental health problems, out of a broad range of family, maternal and pregnancy-related factors, include low maternal education (not completing high school), maternal smoking during pregnancy, gestational hypertension, low family income, and family exposure to stressful life events during pregnancy.
- Low maternal education, low family income, and family exposure to stressful life events during pregnancy also predict increasing mental health problems in children from age 5 to age 14 years.
- Over childhood, family exposure to stressful life events is concurrently related to child mental health, such that boys and girls experiencing higher levels of family stressful events show more mental health problems than children experiencing fewer stressful events.
- The accumulation of stressful family events from early childhood to early adolescence also predicts greater mental health problems in adolescence.

Funders of the project: Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, 'Near Miss' Grant – Karina Allen

Childhood Obesity

INVESTIGATING METHODS FOR MANAGING CHILDHOOD OBESITY

Lisa Gibson

The psychosocial burden of overweight and obesity: There is evidence that overweight and obese children tend to remain overweight or obese into adolescence and adulthood. However, little is known about the long-term psychosocial outcomes of childhood overweight and obesity. This study aimed to investigate the course of psychosocial difficulties over a 2-year period for children who were overweight or obese at baseline, and a comparison sample of children who were a healthy weight at baseline. Overweight and obese children were found to have greater psychosocial distress than healthy weight children, and these differences were more pronounced for girls than boys. Weight and psychosocial functioning both tracked over the 2-year study period, meaning that children who were overweight or obese at baseline tended to remain overweight or obese at the 2-year follow-up, and children with impaired psychosocial functioning at baseline tended to experience ongoing impairments over the next 2 years. This research suggests that overweight and obese children are at risk of ongoing psychosocial distress from middle childhood into early adolescence. The management of childhood obesity needs to attend to psychosocial functioning as well as weight and markers of physical health.

The role of family and maternal factors in the development and persistence of childhood obesity: Treatment programs for childhood obesity have highlighted the importance of the family in treatment. Considering this, it is surprising that few studies have examined the role of family factors in the development of childhood obesity. The objective of this study was to examine which family and maternal factors predict increases in weight in boys and girls during middle to late childhood. Overweight/obese children were recruited from clinical and community settings. A broad range of maternal and family factors were assessed. For children recruited through a community-based setting, maternal Body Mass Index (BMI) and single-parent family structure were significant longitudinal predictors of child BMI z-scores. For children recruited through clinical settings, low family income was the

only significant multivariate predictor of child BMI z-scores. The strong association found between child BMI, maternal BMI and family structure confirms the need to target prevention and intervention efforts for childhood obesity towards families with overweight parents, particularly single-parent families.

Funders of the project: Western Australian Health Promotion Foundation (Healthway).

Autism

WA REGISTER FOR AUTISM SPECTRUM DISORDERS

Emma Glasson, Kavitha Dorairaj, Katherine Russell-Smith, Ainsley Read, Carol Bower.

The aim of the WA Register for Autism Spectrum Disorders is to monitor diagnostic trends of conditions characterized by autism (autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)). These disorders develop in young children and have significant life-long effects in the areas of social interaction, communication and behaviour. The WA Autism Register is ongoing and between 1999 and 2013 information has been collected on more than 4,400 individuals.

Funder of the project:

Government of Western Australia, Department of Health:

Research Staff

Emma Glasson BPsych, BSc (Hons), PhD

Autism Research Team

The Autism Team conduct cutting-edge research into the causes of autism, and discovering new ways to help people with autism live the most fulfilling life possible.

AWARDING OF AUTISM COOPERATIVE RESEARCH CENTRE:

Telethon Kids Institute press release here: http://telethonkids.org.au/news-events/media-releases/2013/february/telethon-institute-a-key-player-in-new-national-autism-research/

Funders of the project. Commonwealth Department of Industry

'CAUSAL' STUDIES SPANNING GENETICS, OBSTETRICS, ENDOCRINOLOGY, NEUROSCIENCE, COGNITION AND BEHAVIOUR.

Conducting 5 Randomized Controlled Trials

1. Oxytocin Nasal Spray

This is a multi-site double-blinded clinical trial investigating whether an oxytocin (OT) nasal spray is an effective treatment for impaired social communication and behaviours in children aged 3-6 years with an Autism Spectrum Disorder (ASD). A total of 100 young children with ASD will be recruited from two sites: 50 participants are expected to be recruited from the Telethon Kids Institute, University of Western Australia and 50 participants from the Brain and Mind Research Institute, University of Sydney.

2. TOBY Playpad App

This is a multi-site single blinded clinical trial of an early intervention program named TOBY (Therapy Outcomes By You) Playpad App for children 4 years or younger with a recent diagnosis of an Autism Spectrum Disorder (ASD). The TOBY is delivered as an educational App on the iPad.

The aims of the TOBY Trial are:

- To determine the effectiveness of TOBY Playpad as a complement to any community therapy a child is receiving, and
- To examine parent empowerment as a result of using the TOBY Playpad App.

A total of 100 children will be recruited from two sites: 50 participants from the Telethon Kids Institute, University of Western Australia and 50 participants from the secondary trial site that is located in Victoria, a collaboration between Deakin, La Trobe and Monash Universities.

3. Fluoxetine: Fluoxetine for the Treatment of Autistic Repetitive Behaviours (FAB Trial)

This is a multi-site randomised double-blind controlled trial of Fluoxetine (Selective Serotonin Reuptake Inhibitor, SSRI) versus placebo. It aims to investigate the efficacy of low dose Fluoxetine on the frequency and severity of restricted, repetitive and stereotyped behaviours among 146 participants aged 7.5-17 years with a confirmed diagnosis of an Autism Spectrum Disorder. Telethon Kids Institute is one of three sites with Murdoch Children's Research Institute, and the Royal Children's Hospital in Melbourne as well as Children's Hospital at Westmead in Sydney being the other trial sites.

4. Bright Light-box therapy

About 50% of individuals with an Autism Spectrum Disorder (ASD) experience sleeping difficulties such as falling asleep or frequent awakenings at night. An intervention trial named 'Bright Light Therapy' is investigating whether scheduled exposure to daily bright light early in the morning may aid in a better sleep at night time among children who are 8-11 years old with a diagnosed ASD.

5. Fish Oil Supplementation Trial

Omega -3 long chain polyunsaturated fatty acids are essential for normal brain development, but some evidence suggest that children with an Autism Spectrum Disorder (ASD) have lesser amounts compared with non-affected children. The use of fish oil supplementation among families who have a child with an Autism Spectrum Disorder is common despite little evidence for its benefits and associated costs. A double blinded randomised controlled trial of fish oil supplementation aims to determine whether the high-dose of fish oil for six months is able to improve behavioural, cognitive or language outcome in children aged 2-6 years with a diagnosed ASD.

Raine Study: Nutrition Group

Professor Wendy Oddy, Dr Gina Ambrosini, Dr Therese O'Sullivan, Dr Monique Robinson, Dr Lucinda Black, Dr Georgina Trapp, Dr Anett Nyaradi, Ms Carly Herbison, Ms Caroline Gallagher

Cardio-metabolic risk factors (obesity, cardiovascular disease, type 2 diabetes, liver injury) and mental health disorders (depression, anxiety, stress) are of increasing population health concern for Australia as well as globally. The primary aim of the nutrition team is to describe relationships between nutritional factors, cardio-metabolic and mental health risk from infancy to adulthood. A wide range of data have been collected in the Raine Study during pregnancy, at birth (n=2868), and at 1, 2, 3, 6, 8, 10, 14 and 17 years of age. The 20 year follow-up is now complete. Existing and newly collected data are being used by the Nutrition team and replication of findings are being reported in collaboration with the Avon Longitudinal Study of Parents and Children (ALSPAC) study in Bristol. The Raine study is ideally placed for a life-course approach in cardio-metabolic and mental health risk. By examining these trajectories of risk to 20 years of age we can identify early determinants risk and key times for intervention.

In 2013 the Nutrition Team were involved in the projects listed below:

DIETARY PATTERNS AND FATTY LIVER DISEASE

Wendy Oddy, Carly Herbison, Peter Jacoby, Gina Ambrosini, Therese O'Sullivan, Oyekoya Ayonrinde, John Olynk, Lucinda Black, Lawrie Beilin, Trevor Mori, Beth Hands, Leon Adams.

Objective: Poor dietary habits have been implicated in the development of non-alcoholic fatty liver disease (NAFLD); however, little is known about the role of specific dietary patterns in the development of NAFLD. We examined prospective associations between dietary patterns and NAFLD in a population-based cohort of adolescents.

Method: Participants in the Western Australian Pregnancy Cohort (Raine) Study completed a food frequency questionnaire at 14 years and had liver ultrasound at 17 years (n = 995). Healthy and Western dietary patterns were identified using factor analysis and all participants received a z score for these patterns. Prospective associations between the dietary pattern scores and risk of NAFLD were analysed using multiple logistic regression.

Results: NAFLD was present in 15.2% of adolescents. A higher Western dietary pattern score at 14 years was associated with a greater risk of NAFLD at 17 years (OR 1.59; 95% CI 1.17,2.14; $p < 0.005$), although these associations were no longer significant after adjusting for body mass index at 14 years. However, a healthy dietary pattern at 14 years appeared protective against NAFLD at 17 years in centrally obese adolescents (OR 0.63, 95% CI 0.41, 0.96; $p = 0.033$), whilst a Western dietary pattern was associated with increased risk of NAFLD. Conclusions: A Western dietary pattern at 14 years was associated with increased risk of NAFLD at 17 years, particularly in obese adolescents. In centrally obese adolescents, a healthy dietary pattern may protect against NAFLD, while a Western dietary pattern may increase the risk of NAFLD.

Funders of the project: NHMRC grants #353514, 403981 and 634445, the Commonwealth Scientific and Industrial Research Organisation and the Australian Heart Foundation / Beyond Blue Strategic Research Initiative (ID G08P4036).

EARLY INFANT FEEDING AND LONG-TERM METABOLIC HEALTH

Wendy Oddy, Rae-Chi Huang, Trevor Mori, Carly Herbison, Meg McHugh, Craig Pennell, Berthold Koletzko, Lawrence Beilin.

This project investigates whether a shorter duration of breastfeeding may be associated with an increased risk of the metabolic syndrome in the long-term later in adolescence. Our objective was to investigate associations between early infant feeding and prevalence of the metabolic syndrome at 17 years as defined by a high-risk metabolic cluster identified in a prospective pregnancy cohort. Infant feeding history was assessed by questionnaire in 2420 children at one year of age participating in The Western Australian Pregnancy Cohort (Raine) Study. Metabolic syndrome was identified at 17 years using a population-derived "high-risk" metabolic cluster variable. We showed that metabolic syndrome prevalence was 17% as classified by the high-risk metabolic cluster. Breastfeeding cessation prior to two months of age was associated with an increased prevalence of the metabolic syndrome at 17 years $p<0.05$. In addition, breastfeeding cessation before two months was associated with high waist circumference as defined by being in the high-risk metabolic cluster (OR 1.43; 95% CI: 1.12-1.82). We concluded from this study supports that a shorter duration of breastfeeding is associated with a higher prevalence of the metabolic syndrome in adolescence.

Funders of the project: NHMRC-EU collaborative project 1037960 (funded 2012-2016).

This research has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013), project Early Nutrition under grant agreement n°289346.

NUTRITIONAL DETERMINANTS OF CARDIO-METABOLIC AND MENTAL HEALTH RISK

Wendy Oddy, Therese O'Sullivan, Rae-Chi Huang, Trevor Mori, Gina Ambrosini, Peter Jacoby, Carly Herbison, Meg McHugh, Leon Adams, Lawrence Beilin, Gina Trapp, Lucinda Black, Caroline Gallagher.

Cardio-metabolic and mental health disorders are of increasing population health concern for Australia as well as globally. The primary aim of this project is to describe relationships between nutritional factors, cardio-metabolic and mental health disorders from infancy to adulthood. A wide range of data have been collected in the Raine Study during pregnancy, at birth (n=2868), and at 1, 2, 3, 6, 8, 10, 14 17 and 20 years of age. Existing and newly collected data are being used and replication of findings are being reported in collaboration with the Avon Longitudinal Study of Parents and Children (ALSPAC) study in Bristol. The Raine study is ideally placed for a life-course approach in cardio-metabolic and mental health disorders. By examining these trajectories to 20 years of age we can identify early determinants of risk and key times for intervention.

Funders of the project: NHMRC 1022134 (funded 2012-2014).

NUTRITIONAL DETERMINANTS OF COGNITIVE DEVELOPMENT

Anett Nyaradi, Wendy Oddy, Siobhan Hickling, Jianghong Li, Jonathan Foster, Andrew Whitehouse.

In this PhD project Dr Anett Nyaradi is investigating relationships between dietary intake and cognitive and educational performance in a cohort of Western Australian children to 17 years, and contribute to a growing body of knowledge concerning diet, cognitive development (as measured by CogState) and educational outcome.

The specific aims of the project are to:

1. Conduct a comprehensive literature review on diet, cognitive development and educational outcome.
2. Investigate the relationship between early dietary intake as a diet quality score and specific food group scores (years 1, 2 and 3) and cognitive outcome in childhood (years 5, 8 and 10).
3. Examine the relationship between early childhood diet as a diet quality score and specific food group scores (years 1, 2 and 3) and cognitive development (as measured by CogState) in adolescents at age 14 and 17.
4. Investigate the relationship between adolescent diet quality (years 14 and 17) and CogState (years 14 and 17).
5. Investigate the relationship between specific food groups, nutrients and academic achievement of 14 years old adolescents.

Dr Nyaradi has received a UWA APA scholarship and a Raine Study scholarship to conduct this PhD Project (2012-2014).

Social determinants of child health/social epidemiology

PARENTAL WORK HOURS AND CHILD MENTAL HEALTH

Chief Investigators: Jianghong Li, Lyndall Strazdins, Garth Kendall

The research has been published as follows:

Sarah Johnson, Jianghong Li, Garth Kendall, Lyndall Strazdins, Peter Jacoby. Mothers' and Fathers' Work Hours, Child Gender and Behavior in Middle Childhood. Journal of Marriage and Family, 2013, 75: 56-74.

Jianghong Li, Sarah Johnson, Wen-Jui Han, Andrews S, Dockery M, Kendall G and Strazdins L. Parents' nonstandard work and child wellbeing: A critical review of the literature. Journal of Primary Prevention 2014, 35 (1): 53-73 (DOI: 10.1007/s10935-013-0318-z).

Funded by The Foundation for Children 2010-2012

MATERNAL STRESSFUL EVENTS IN PREGNANCY AND NUMERACY AND LITERACY AT GRADE FIVE

Jianghong Li, Monique Robinson, Anke van Eekelen, Jonathan Foster, Eva Malacova.

This study examines the timing and number of stressful events in pregnancy and their link with numeracy and literacy achievement in a subset of the Raine Cohort children in grade 5 who attended government schools in WA. The aim of the study is also to demonstrate the importance of examining gender difference in the impact of maternal stressful events in pregnancy on offspring's school achievement and to elucidate the need to distinguish between confounding factors from mediating factors in the causal pathway.

This work has been published as follows:

Jianghong Li, Monique Robinson, Eva Malacova, Peter Jacoby, Jonathan Foster, Anke van Eekelen. Maternal life stress events in pregnancy link to children's school achievement at age 10. Journal of Pediatrics, 2013 162 (3), 483-489. Impact factor: 4.115, ERA ranking: A, Category ranking: 4/113 (Q1). http://dx.doi.org/10.1016/j.jpeds.2012.09.007

HOUSING AND CHILDREN'S HEALTH AND DEVELOPMENT

M Dockery, G Kendall, J Li, L Strazdins, F Chan, R Ong, R Seymour, A Mahendran

This is a scoping study that provides a review of international research literature on the link between housing and children's health and development and it proposes a research plan for developing this area of research in Australia. Further funding has been obtained from Australian Housing and Urban Research Institute to carry out the research plan in 2011 and beyond. The project will investigate the effect of housing location and housing quality and ownership on child developmental outcomes.

Funders of the project: Australian Housing and Urban Research Institute

This research has been published as follows:

A.M. Dockery, R. Ong, S. Colquhoun, J Li, G. Kendall. Housing and Children's Development and Wellbeing: Evidence from Australian Data. A Final Report to Australian Housing and Urban Research Institute. June 2012 (peer reviewed). ISSN: 1834-7223.

PARENTAL WORK HOURS AND CHILD BMI

Jianghong Li, Wendy Oddy, Sarah Johnson, Garth Kendall, Fiona Stanley

The study investigates the association of mother's and fathers' work hours and child BMI (ages 1 to 10) in the Raine Cohort. The study addresses the current issues and research gaps in the field, using advanced analytical models.

Project status: The analysis has been finalised and the paper will be completed in June 2014.

MOTHERS" WORK HOURS AND ADOLESCENT DEPRESSION

Jianghong Li, Sarah Johnson, Lyndall Strazdins, Garth Kendall, Peter Jacoby.

The study examines the link between maternal work status and hours (in early and middle childhood and adolescence) and depression in adolescents at age 14, based on the Raine Study

Cohort data.

Project status: some further analysis is required to finalise the results

PARENTAL WORK AND CHILD HEALTH AND DEVELOPMENT

Jianghong Li (Germany and WA), Garth Kendall, Lyndall Strazdins, Mike Dockery, Sarah Johnson, Rachel Skinner, Wen-Jui Han (The US).

The project aims to investigate the impact of parental employment status and non-standard work schedules on the health and wellbeing of Australian children/adolescents and to shed new light on the social and economic causes of the high prevalence of mental health problems in today's children. The proposed research is based on data from Longitudinal Study of Australian Children (LSAC) and the Western Australian Pregnancy Cohort Study (Raine). The project draws on multidisciplinary expertise from sociology, social epidemiology, developmental epidemiology, clinical psychology and labour economy. We have published a comprehensive review of the literature on non-standard work schedule and child mental health and behavioural problems and the review informs us about specific research aims and questions. This program of research investigates the following outcomes: Mental health, risk taking behaviours, and school achievement.

Project status: Ongoing

Jianghong Li (Germany and WA), Matthias Pollmann-Schult (Germany)

This study examines the link between father's and mother's commute to work place and child social and emotional wellbeing, using the German Socioeconomic Panel Study data (Since 1984).

Project stage: A paper is near submission to an international peer reviewed journal.

Jianghong Li (Germany and WA), Matthias Pollmann-Schult (Germany)

This project examines the link between father's and mother's non-standard work schedules and social and emotional wellbeing in children ages 5-6, using nationally representative data from the German Socioeconomic Panel Study (Since 1984).

Project stage: ongoing

Jianghong Li (Germany and WA), Matthias Pollmann-Schult (Germany), Lyndall Strazdins (ANU)

This project aims to examine the link between parent job quality and child emotional and behavioural problems, using the German Socioeconomic Panel Study data (Since 1984).

Project stage: Ongoing

Staff and Students 2013

RESEARCH STAFF

Dr Karina Allen, PhD, MPsych (Clinical), BA (Hons)

Kirsten Alpers

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Dr Alison Anderson, BSc (Hons), GradDipPH, PhD

Denise Anderson, BSc

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Katrina Boterhoven de Haan, BPsych (Hons)

Jenny Bourke, BE, MPH

Winthrop Research Professor Carol Bower MBBS, MSc, PhD, FAFPHM, DLSHTM, FFPHA

Rhonda Breen Bsc MPsych

Dr Sally Brinkman, PhD, BA, MPH

Jessinta Brown BSc GradDipExSci

Kaashifah Bruce

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Daniel Christenson, BAPsych(Hons) Grad Cert Applied Statistics

Dr Kim Clark, BSc, Grad Dip Bus, PhD

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Rachel Collins PhD

Deirdre Croft, BA, Dip Criminology

Lyn Colvin, BCom, MPH

Matthew Cooper, BCA/BSc

Denny Craig, DipSecStudies

Deirdre Croft, BA, Dip Criminology

Michelle de Klerk

Professor Nick de Klerk, BSc, MSc, PhD

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Dr Jenny Downs, BApplSci (Physio), MSc, PhD

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Natalie Eiffler, BSc (Health Information Management)

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Anna Fletcher, BSc (nutrition) PGDip (dietetics)

Caroline Gallagher, BSc

Sharon Gam BSc

Dr Lisa Gibson, BA (Hons)MPsych, PhD

Dr Sonya Girdler, PhD

Dr Emma Glasson, BPsych, BSc(Hons), PhD

Dr Rebecca Glauert, BPsych(Hons), PhD

Jo Granich, BSc MPH

Sue Green

Dr Kathryn Greenop, PhD

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Katherine Hafekost, BSc(Hons)

Dr Geoffrey Hammond, BSc, PhD

Kirsten Hancock, BA(Hons) MSc (Applied Statistics)

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Natasha Haynes, BSc (Hons)

Dr Tamika Heiden, BSc, PhD

Carly Herbison, BSci

Anke Hoskins, MPH

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Tanyana Jackiewicz, BSc(Hons) MPH

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Dr Sarah Johnson, PhD

Timothy Johnson

Heather Jones, B.Ed

Dr Angela Kinnell, PhD, BHSc(Hons), BA

Dr Amanda Langridge, BSc (Math.Sci), BSc(Hons), PhD

Professor David Lawrence, BSc, PhD, ATCL

Associate Professor Deborah Lehmann, MBBS, MSc

Assoc. Clin. Professor Helen Leonard, MBChB, MPH

Ruth Leong BSc MPH

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Miriam Maclean

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Francis Mitrou, BEc

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Rosemary Wyber, MBChB, MPH

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Chi Le Ha, MBBS, PhD Candidate

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Kirsten Hancock, BA (Hons), MSc (Applied Statistics). PhD Candidate.

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Rachel Jones, Honours

Nicholas Lillyman, Honours

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Sandra Louise, PhD candidate, UWA

Miriam Maclean, PhD candidate, UWA

Richard Maganga, MBBS, PhD Candidate

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Caitlin Marr, Post Grad Diploma candidate, Curtin

Charlotte McKnight, Masters

Aniket Mishra

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Priyakumari Ganesh Parmar MSc, PhD Candidate

Glenn Pearson, BA(Education), PhD candidate, UWA

Bianca Petterson, Doctorate (psychology)

Erin Pettitt, Honours

Sebastian Rauschart, PhD Candidate

Karen Richards, Doctorate (clinical physiotherapy)

Marie Rye BSc (Hons), PhD Candidate

Carrington Shepherd, PhD candidate, Curtin

Dr Desiree Silva, MBBS, FRACP, MPH, PhD candidate, UWA

James Slater, Masters

Ms Amelia Stephens, PhD candidate

Yonit Stoch, Honours

Alex Tan, Masters

Ms Diana Tan, PhD candidate

Lauren Taylor, PhD candidate, UWA

Jessica Tearne, PhD candidate, UWA

Michelle Trevanan, Honours

Lisa Unwin, PhD candidate, UWA

Anna Urbanowicz, BSc(OT)(Hons), PhD candidate ECU

Stephanie Wade, PhD candidate, UWA

Robert Waller, MManipTher, BSc Physio, PhD Candidate

Elisha White, MHltSci BSc BA CRFS, PhD Candidate

Scott White, MBBS, PhD Candidate

Janice Wong, BSc (Psych) (Hons), PhD candidate, UWA

Kingsley Wong, MBBS MBA MSc AFCHSM, MPH candidate, UWA, M Medical Statistics candidate

Paula Wyndow, BSc Postgraduate Diploma, PhD candidate, Curtin

Seyhan Yazar, BMedSci MOrth, PhD Candidate

THESES PASSED

Alison Anderson, PhD, University of Western Australia, Bioinformatics Approaches for Investigating Toxicant-Induced Endocrine Disruption of the Epigenome

Geeta Appannah, PhD, University of Cambridge UK, Dietary patterns, obesity and cardiovascular risk factors in young people

Sally Brinkman, PhD, University of Western Australia, School of Paediatrics and Child Health. Thesis titled: "The validation and use of a population measure of early childhood development in Australia: the Australian Early Development Index."

Anna Ferrante, PhD, University of Western Australia. Juvenile delinquency, developmental criminology, criminal career research, Indigenous involvement in the criminal justice system.

Michele Hansen, PhD, University of Western Australia, Assisted Reproductive Technology and adverse child health outcomes.

Caitlin Marr BSc (PT) (Hons) Curtin University, Recovery following spinal fusion in girls with Rett syndrome and their families

Julie Marsh, PhD, University of Western Australia, Association of validated breast cancer susceptibility single nucleotide polymorphisms (SNPs) and modifiable childhood traits

Marie Rye, PhD, University of Western Australia, Genetic Susceptibility to Otitis Media in Western Australia

Carrington Shepherd. PhD, Curtin University of Technology. Socieconomic gradients in Western Australian Indigenous child health.

Lauren Taylor, PhD, University of Western Australia, An investigation of the phenotypic and etiological relationship between autism and specific language impairment.

Ryan Van Lieshout, PhD, McMaster University, Ontario, Canada, The Mental Health of Youth Born at High Birth Weight and Subjected to their Maternal Determinants: A Multi-National Study of Prospective, Longitudinal Cohorts

Nicolle Warrington, BSc (Hons) PhD, University of Western Australia, Modelling of complex longitudinal phenotypes over childhood: Growth trajectories in the developmental origins of health and disease

Lydia Windsor, Bachelor of Medical Science, University of Notre Dame, An investigation of an extended run of homozygosity at chromosome Xp11.21 in females with autism spectrum disorder

Awards

Professor Jonathan Carapetis, Project "A case control study of rotavirus vaccine effectiveness against gastroenteritis hospitalization of children in the NT" selected as one of the "Ten of the Best" NHMRC-funded projects in Australia.

Professor Jonathan Carapetis, T. Duckett Jones Memorial Lecturer (American Heart Association) Texas, USA.

Professor Jonathan Carapetis, Honorary Doctor of Science, Charles Darwin University, NT.

Jenny Fairthorne, ASID Student Travel Bursary, August 2013

Jenny Fairthorne, St Vincent's Student Society Travel Award, 2013

Jenny Fairthorne, UWA Travel Award, June, 2013

Jenny Fairthorne, Women's and Infants' Research Foundation Award, June, 2013

Stephanie Fehr, Friends of the Institute Travel Award, 2013

Stephanie Fehr, Stan Perron Award for Excellence, 2013

Hannah Moore, Western Australian Young Tall Poppy Science Award

Wendy Oddy, Telethon Institute For Child Health Research Scientist Leadership Award

Monique Robinson, New Independent Researcher Infrastructure (NIRIS) Award

Monique Robinson, "40 under 40" award

Thomas Snelling, Fiona Stanley Investigator, Telethon Institute for Child Health Research: 2013-2015

Anna Urbanowicz, Three Minute Presentation Winner at the 7th Annual Student Circle Symposium, Telethon Institute for Child Health Research $500

Andrew Whitehouse, Patron, Kids are Kids Therapy and Education Centre

Andrew Whitehouse, Best Abstract at ' American Society of Anesthesiologists' conference (first author: Caleb Ing)

Andrew Whitehouse, Best Abstract at 'Eating Disorders Research Society' Conference (first author: Karina Allen)

External Committees

INTERNATIONAL

Christopher Blyth, Vaccines Working Group, International Society of Chemotherapy (2012-current)

Carol Bower, International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Nominating Committee

Carol Bower, Faculty member, Training Program in Birth Defects Surveillance, run jointly by WHO, CDC and ICBDSR

Professor Jonathan Carapetis, 2011- Editorial Board Member, Global Heart Journal, World Heart Federation and Elsevier.

Professor Jonathan Carapetis, 2011- Working Group on Rheumatic Fever and Rheumatic Heart Disease, World Heart Federation, Geneva.

Professor Jonathan Carapetis, 2008- Expert Group Core Member and Head, Expert Group on Rheumatic Heart Disease, Cardiovascular Diseases Expert Group, Global Burden of Diseases, Injuries, and Risk Factors Study.

Kitty Foley, Student Representative, IAASSID International Family Special Interest Research Group, 2012-

Lisa Gibson, United Way WA -- Community Impact and Allocations Committee. Commenced January 2012

Deborah Lehmann, Papua New Guinea Institute of Medical Research Buttressing Coalition member 1998-

Deborah Lehmann, Member of Conference Committee for the 19th International

Symposium on Recent Advances in Otitis Media (RAOM) (2012-)

Helen Leonard, Member of Executive of RettSearch, International Consortium of Rett Syndrome Clinical Researchers (2009-)

Wendy Oddy, International Consultative and Advisory Committee, Early Nutrition

Wendy Oddy, Recommendations Development Panel, Early Nutrition Project, Munich, Germany

Wendy Oddy, Scientific Advisor, Early Nutrition Academy, University of Munich, Germany

Melissa O'Donnell, International Society for the Prevention of Child Abuse and Neglect (2007-present)

Melissa O'Donnell, International Child Maltreatment Data Working Group (2009-present)

NATIONAL

Christopher Blyth, Australian Technical Advisory Group on Immunisations (ATAGI), Australian Government: Department of Health and Aging (2012-current)

Christopher Blyth, ATAGI Pneumococcal Working Party Australian Government: Department of Health and Aging (2013-current)

Christopher Blyth, ATAGI Varicella / Zoster Working Party, Australian Government: Department of Health and Aging (2013-current)

Christopher Blyth, Pneumococcal Disease Advisory Group, Influenza Specialist Group (2013-current)

Christopher Blyth, Australian and New Zealand Mycology Interest Group Business Committee, Australasian Society for Infectious Diseases

Christopher Blyth, Australasian Stewardship of Antimicrobials in Paediatrics Group, Australasian and New Zealand Paediatric for Infectious Diseases Group

Carol Bower, National Perinatal Statistics Unit Steering Committee for Congenital Anomalies

Carol Bower, Australian Paediatric Surveillance Unit Scientific Review Panel

Carol Bower, National Perinatal Epidemiology and Statistics Unit Fetal Alcohol Spectrum Disorder

Sally Brinkman, Vice President of the Board, Playgroups Association of South Australia

Sally Brinkman, Member, South Australian Human Research Ethics Committee

Professor Jonathan Carapetis, 2012- Member, Australian Institute of Company Directors.

Professor Jonathan Carapetis, 2012- Member, Program Management Committee, RHD Australia.

Professor Jonathan Carapetis, 2010- Board Member, One Disease at a Time Foundation.

Professor Jonathan Carapetis, 2007- National Committee for Medicine, Australian Academy of Science.

Brad Farrant, Australian Research Alliance for Children and Youth's representative on the Climate and Health Alliance's committee of management, 2013

Rebecca Glauert, Closing the Gap Clearinghouse. Board member- 2013 to present

Yasmin Harman-Smith, Deputy Chair of the Board, Gowrie South Australia

Tanyana Jackiewicz, National Child and Community Health Council since 2008

Heather Jones, Australasian FASD Conference Organising Committee 2012-2013

Heather Jones, Australasian FASD Conference Stakeholder Advisory Group 2012-2013

Deborah Lehmann, Data safety monitoring board of CHiRRP "Combating H. influenzae related respiratory pathology" (2012-)

Helen Leonard, Member of Executive, Australian Association of Developmental Disability Medicine, (2002-)

Raewyn Mutch, Australasian FASD Conference Stakeholder Advisory Group 2012-2013

Raewyn Mutch, The 4th Transcultural Mental Health and 2nd Refugee Health Conference, Perth, Western Australia from 31 October to 1 November, 2013

Wendy Oddy, Preventive and Community Health Committee, NHMRC, Invited position

Wendy Oddy, NHMRC Research Translation Faculty, invited position

Thomas Snelling, Economics Sub Committee of the Pharmaceutical Benefits Advisory Committee, Feb 2013 – current

Cate Taylor, Sustained Nurse Home Visiting Project (right@home) (ARACY and the Centre for Community Child Health), Member of the Expert Reference Group

Cate Taylor, right@home-wrap (The Australian Research Alliance for Children and Youth). Member of the Expert Reference Group

Cate Taylor, Australian Research Alliance for Children and Youth (ARACY), Councillor

Cate Taylor, Economic Modeling of Childhood Interventions. Department of Education and Child Development, Adelaide, South Australia. Member of the Expert Reference Group

Rochelle Watkins, Board Member, The National Organisation for Fetal Alcohol Spectrum Disorders Australia

Andrew Whitehouse, Board Member, Australian Society for Autism Research

LOCAL

Christopher Blyth, WA Tuberculosis Advisory Council, Health Department of Western Australia

Christopher Blyth, Infection Control Committee, Princess Margaret Hospital for Children

Christopher Blyth, Safe Design Advisory Committee, New Children's Hospital, Perth

Jenny Bourke, Director, Board of Kalparrin (Parents of Children with Special Needs Inc) (since 2009)

Jenny Bourke, Member, Scientific Advisory Committee, SIDS and KIDS WA (since 2011)

Carol Bower, Perinatal and Infant Mortality Committee Department of Health WA

Carol Bower, Prenatal Diagnosis Committee, Department of Health WA

Professor Jonathan Carapetis, 2013- Member, Western Australian Immunisation Strategy Implementation Steering Committee (WAISISC).

Professor Jonathan Carapetis, 2013- Chair, Clinical Advisory Group, WA RHD Control Program.

Professor Jonathan Carapetis, 2012- Member, Western Australian State Health Research Advisory Council (SHRAC).

Professor Jonathan Carapetis, 2012-13 Member, The University of Western Australia, Faculty Strategic Research Advisory Group (SRAG).

Professor Jonathan Carapetis, 2008-13 Member, Advisory Board Australian Indigenous HealthInfoNet.

Jenny Downs, Human Research Ethics Committee, Princess Margaret Hospital for Children (2010 -).

Jenny Downs, Committee Member, Consumer and Community Advisory Council, Telethon Institute for Child Health Research (2012 -)

Rebecca Glauert, Ngala Professional Advisory Committee (2011 – present)

Rebecca Glauert, Data Linkage Advisory Board (2010 – present)

Michele Hansen, Reproductive Technology Council, December 2012

Anke Hoskins, Meningitis Centre Management Committee (2012-)

Anke Hoskins, Infectious Diseases Community Reference Group (2012-)

Tanyana Jackiewicz, Commissioner for Children and Young People Expert Reference Group: Wellbeing Indicators Group since 2009

Tanyana Jackiewicz, Commissioner for Children and Young People Building Blocks Working Party (2013)

Tanyana Jackiewicz, Child and Youth Health Network, Executive Advisory Group since 2006

Heather Jones, Injury Control Council of Western Australia, Alcohol and Pregnancy Peer Educator Project, Steering Group 2013-2014

Heather Jones, Organising Committee 'Focus on FASD Prevention' Forum 2012-2013

Deborah Lehmann, Perinatal and Infant Mortality Committee, Ministry for Health, WA, Deputy to Carol Bower (2005-)

Deborah Lehmann, Meningitis Centre Management Committee (1998-)

Deborah Lehmann, Infectious Diseases Community Reference Group (2008-)

Helen Leonard, Women's and Newborns' Health Network Executive Advisory Group

Helen Leonard, Executive Committee Perth Epidemiology Group, (2008-)

Miriam Maclean, Perinatal Mental Health Services Research Committee (July 2010 – present)

Miriam Maclean, Marce Society Conference Local Organising Committee (January 2011 – present)

Hannah Moore, Infectious Diseases Community Reference Group, 2007-present

Raewyn Mutch, Representative of Princess Margaret Hospital on the WA Department of Health and Telethon Institute ACCARE study into the outcomes and care of Women and Infants attending the West Australian Newborn Drug and Alcohol Service (WANDAS) of King Edward Memorial Hospital (KEMH). 2013

Raewyn Mutch, Representation of PMH Refugee Health Service for the Model of Care for the management of women with Female Genital Mutilation. 2013

Jan Payne, Panel Member, Alcohol Advertising Review Board 2013

Glenn Pearson, Health Consumer Council of Western Australia

Glenn Pearson, Curtin University Human Research Ethics Committee

Glenn Pearson, Telethon Institute for Child Health Research Consumer and Community Advisory Council

Glenn Pearson, Key Aboriginal Advisory Group, Strong Spirit Strong Future - Promoting Healthy Women and Pregnancies 2011

Glenn Pearson, Meningitis Centre Committee 2012

Desiree Silva, Head of Department Medical Advisory Committee (HOD/MAC) Joondalup Health Campus

Desiree Silva, Chair of the Royal Australasian College of Physicians

Desiree Silva, State Paediatric Implementation Plan

Thomas Snelling, Western Australia Committee on Antimicrobials, April 2013 - current

Thomas Snelling, Children's Hospital Antimicrobial Management Program Steering Committee (Chair), Feb 2013- current

Anna Urbanowicz, Research and Development Committee Member, WA Occupational Therapy Association (2012 -)

Claire Waddington, The Biological Hazards Committee, Telethon Kids Institute, (2013 – current)

Rochelle Watkins, Member Board of Directors, Neurological Council of Western Australia

Andrew Whitehouse, Board Member of the Western Australian Autism Diagnosticians' Forum

Janice Wong, The Australian Association of Cognitive Behavioural Therapy (December 2010)

Kingsley Wong, Perth Epidemiology Group – Treasurer, start date 1/1/2013 (committee member since 4/2012)

Invited Presentations

INTERNATIONAL

Steve Ball, Spatial modelling of patient behaviour. Cooperative Centre for Spatial Information Conference, Christchurch, New Zealand, Nov 20-21, 2013

Christopher Blyth, Influenza Vaccines: Past, Present and Future. SAFEVIC, Clinical Vaccinology Update, 2013

Christopher Blyth, Invasive Fungal Infection in Transplant Recipients, IDWeek, San Francisco, 2013

Christopher Blyth, Never work with Children and Animals: Invasive fungal infections in children, Mycology Masterclass VI, Kingscliff, 2013

Christopher Blyth, Prevention and Control of Healthcare Associated Infection Outbreaks by Vaccines, International Congress of

Chemotherapy and Infection, Yokohama Japan 2013

Christopher Blyth, Epidemiology and clinical background to invasive meningococcal disease International Congress of Chemotherapy and Infection, Yokohama Japan 2013

Carol Bower, Prevention of neural tube defects in Australia – how are we doing? International Congress of Pediatrics, August 2013

Carol Bower, FASD in Australia – approaches to research. International Congress of Pediatrics, August 2013

Carol Bower, Developmental Outcomes of Children of Mothers with an Alcohol-Related Diagnosis. International Congress of Pediatrics, August 2013

Carol Bower, Folate update. International Clearinghouse for Birth Defects Surveillance and Research Annual Meeting. Dec 2013

Carol Bower, Oesophageal atresia and tracheo-oesophageal fistula in Western Australia: prevalence, trends and associated anomalies. International Clearinghouse for Birth Defects Surveillance and Research Annual Meeting. Dec 2013

Carol Bower, Exploring the potential to use data linkage for investigating the relationship between birth defects and prenatal alcohol exposure. International Clearinghouse for Birth Defects Surveillance and Research Annual Meeting. Dec 2013

Sally Brinkman, Measurement of change in the EDI within Australia: strategies to communicate community level change in developmental vulnerability. In M. Janus (Chair), Exploring change in children's developmental outcomes over time: community, state/province, and international stability. Symposium conducted at the meeting of the Society for Research in Child Development, Seattle, USA, 18-20 April 2013

Jeff Cannon, Social inequality and hospitalisation costs for the first year of life of preterm infants. Developing a Data Linkage System to Enable Innovative Research. Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Professor Jonathan Carapetis, Infection and Immunity in Children International Congress of Paediatric Infectious Disease, Oxford, UK.

Professor Jonathan Carapetis, Group A Streptococcal Disease Vaccine Workshop, Auckland, NZ.

Professor Jonathan Carapetis, 6th World Congress Paediatric Cardiology and Cardiac Surgery, Cape Town, SA.

Professor Jonathan Carapetis, Acute Rheumatic Fever Symposium, Wellington, NZ.

Nick De Klerk, Technical and practical aspects of cross agency data linkage: The West Australian example. Developing a Data Linkage System to Enable Innovative Research Conference. Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Jenny Downs, Development and motor function in Rett syndrome, Shenzhen – Sino-Australian Rett Syndrome Meeting, Shenzhen Children's Hospital, Shenzhen, China, March 2013

Jenny Downs, Scoliosis: what does it mean for those affected by Rett syndrome. 3rd European Rett Syndrome Conference, Maastricht, Netherlands, October 2013

Brad Farrant, Cognitive Flexibility, Theory of Mind and Hyperactivity/Inattention. British Psychological Society Joint Cognitive Psychology Section & Developmental Psychology Section Annual Conference, 4-6 Sept 2013, Reading University, UK

Stephanie Fehr, Treatment Regimens for Epilepsy in children and adults with the CDKL5 disorder, 3rd European Rett Syndrome Conference, Maastricht, Netherlands, October 2013

Rebecca Glauert, Linking data to build an evidence base: The WA Developmental Pathways Project. Developing a Data Linkage System to Enable Innovative Research Conference. Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Tess Gregory, Measurement of change in the EDI within Australia: strategies to communicate community level change in developmental vulnerability. In M. Janus (Chair), Exploring change in children's developmental outcomes over time: community, state/province, and international stability. Symposium conducted at the meeting of the Society for Research in Child Development, Seattle, USA, 18-20 April 2013

Heather Jones, How Consumer and Community Participation Influences FASD Research. 5th International FASD Conference: Research, Results and Relevance: Integrating research, policy and promising practice around the world, Vancouver March 2013

Helen Leonard, Rett syndrome from a global perspective. Chinese Rett syndrome Family Association meeting, Shenzhen, China, March 2013

Helen Leonard, Alison Anderson. MECP2 Duplication International Database. 2nd MECP2 Duplication Syndrome Family Conference, Houston, USA, March 2013

Helen Leonard, Translating research findings into improved outcomes for those affected by Rett syndrome: where are we in this journey? 3rd European Rett Syndrome Conference, Maastricht, The Netherlands, October 2013

Sarah McIntyre, A Population Study of Etiology of Cerebral Palsy (CP) in Term and Late Preterm Singletons: Birth Defects, Are They the Next Frontier? Pediatric Academic Societies 2013; Washington DC

Sarah McIntyre, Birth defects and growth restriction in term cerebral palsy. Neonatal Encephalopathy: Advancing the Science and improving outcomes 2013; National Institutes of Health, Washington DC

Sarah McIntyre, Aetiology of HIE in CP. Castang Foundation Workshop on the aetiology, prevention and treatment of Hypoxic Ischaemic Encephalopathy 2013; London

Raewyn Mutch, Knowledge, attitudes and practices for FASD across the justice systems of Western Australia. 5th International FASD Conference: Research, Results and Relevance: Integrating research, policy and promising practice around the world, Vancouver March 2013

Jan Payne, Alcohol and pregnancy: disparity between women's informational expectations and obstetricians' and general practitioners' practice. 5th International FASD Conference: Research, Results and Relevance: Integrating research, policy and promising practice around

the world, Vancouver, March 2013

Marcela Quintero, Developmental Pathways Project: Challenges for the WA data linkage system. Developing a Data Linkage System to Enable Innovative Research. Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Desiree Silva, Early Risk factors and education and justice outcomes of children diagnosed and treated for ADHD in Western Australia: Population Linkage Study. Invited speaker for a South East Asian and Australian perspective on ADHD. 4th World ADHD Congress, Milan, Italy May 2013

Scott Sims, Using mapping to identify socio-demographic inequalities in mental health and educational outcomes. Developing a Data Linkage System to Enable Innovative Research Conference, Berlin, Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Anna Urbanowicz, Speech and language abilities before and after regression in 1011 girls and women with Rett syndrome. 3rd European Rett Syndrome Conference, Maastricht, The Netherlands, October 2013

Rochelle Watkins, Development of an instrument for the diagnosis of fetal alcohol spectrum disorders in Australia. 5th International FASD Conference: Research, Results and Relevance: Integrating research, policy and promising practice around the world, Vancouver March 2013

Janice Wong, Using mapping to identify socio-demographic inequalities in mental health and educational outcomes. Developing a Data Linkage System to Enable Innovative Research Conference, Berlin, Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Steve Zubrick, Growth models of academic performance and school attendance – Does every day count? The Royal Swedish Academy of Sciences, Stockholm. October 23 2013

NATIONAL

Eve Blair, Understanding cerebral palsy. Course on Cerebral Palsy conducted by the International Society for Prosthetics and orthotics. Perth, October 2013

Eve Blair, Antecedents of intrapartum stillbirth and neonatal deaths in singletons born after 35 weeks gestation. April 2013. Annual meeting of the PSANZ PMG and ANZSA (Australia and New Zealand stillbirth alliance)

Eve Blair, Pathways to cerebral palsy in singletons born >=35 weeks gestations. Keynote address, annual conference of Perinatal Societies of Australia and New Zealand, Adelaide 2013

Sally Brinkman, AEDI 2012 Embargoed Results. Invited Presentation to the Executive Leaders Group. Department of Education and Child Development, Adelaide, Australia. February 2013

Sally Brinkman, AEDI 2012 Embargoed Results. Invited Presentation to the Senior Officers Group. Department of Education and Child Development. Adelaide, Australia, March 2013

Sally Brinkman, AEDI 2012 Embargoed Results Briefing, Invited Presentation to SA senior level stakeholders across government and non-government. Adelaide, Australia, April 2013

Sally Brinkman, Invited lecture. What is the magnitude of inequality in child development across Australia and how does this differ across jurisdictions – implications for policy and service delivery? AEDI Coordinating Committee for Tasmania and invited guests. Hobart, Tasmania. November

Sally Brinkman, Invited keynote. What is the magnitude of inequality in child development across Australia and how does this differ across jurisdictions – implications for policy and service delivery? Our Health – Who Decides Conference organised by the Social Determinants of Health Advocacy Network. Hobart, Tasmania. November 2013

Sally Brinkman, Invited keynote. What does the AEDI tell us about how well our community supports our children? Community Forum. Mount Gambier, South Australia. July 2013

Professor Jonathan Carapetis, Charles Darwin University Occasional Address, Darwin NT.

Daniel Christensen, Human Capability Development Across the Lifecourse. Invited Seminar, School of Social Science, University of Queensland, February 2013

Daniel Christensen, Nicholson, J. Risk factors associated with fathers' persistent psychological distress across the early parenting period. LSAC Conference, Melbourne November 2013

Tess Gregory, Parenting Influence on the Association between Temperament and IQ. Poster presented at the Infant and Early Childhood Social and Emotional Wellbeing Conference, Canberra, Australia, 30 Oct – 2 November 2013

Kirsten Hancock, Student attendance and educational outcomes: every day counts. Department of Education, Employment and Workplace Relations, Canberra. February 28 2013

Yasmin Harman-Smith, Children's Centre Qualitative Evaluation Findings. Invited Presentation to the Children's Centre Operations group. Adelaide, Australia. June 2013

Yasmin Harman-Smith, Children's Centre Qualitative Evaluation Findings. Invited Presentation to the Early Child Development Strategy group. Adelaide, Australia. June 2013

Yasmin Harman-Smith, Children's Centre Qualitative Evaluation Findings. Invited Presentation, Children's Centre Leadership Development Program. Adelaide, Australia. August 2013

Yasmin Harman-Smith, Children's Centre Qualitative Evaluation Findings. Invited Presentation, Fraser Mustard Peer Review Session. Adelaide, Australia. October 2013

Nan Hu, Socioeconomic disadvantage, parental mental health and deliberate self-harm and suicidal death in young people: a birth cohort study using record linkage. Developing a Data Linkage System to Enable Innovative Research Conference. Germany, Berlin Social Research Center (WZB), Berlin, Germany, September 2013

Heather Jones, Involving consumers and the community in FASD research in Australia. Australasian FASD Conference, Brisbane November 2013

David Lawrence, Student attendance and educational outcomes: every day counts. Department of Education, Employment and Workplace Relations, Canberra. February 28 2013

Deborah Lehmann, Confronting the killer: epidemiology and prevention of pneumonia in Papua New Guinean children. The Lung Institute of Western Australia Medical Research Seminar; Nov 18 2013; Perth WA

Sarah McIntyre, Population studies contributing to the prevention of cerebral palsy. Research briefing of Cerebral Palsy Research Foundation 2013; Sydney

Miriam Maclean M, Entering and leaving out of home care during childhood: Cumulative incidence study of groups most at risk. Developing a Data Linkage System to Enable Innovative Research Conference, Social Science Research Center (WZB) Berlin, Germany, September 2013

Francis, Mitrou, Human Capability Development Across the Lifecourse. Invited Seminar, School of Social Science, University of Queensland, February 2013

Raewyn Mutch, FASD and Justice. Probation and Community Corrections Officers Conference, Alice Springs October 2013

Raewyn Mutch, Fetal Alcohol Spectrum Disorder. Australian Forensic Psychologists Conference, April 2013.

Raewyn Mutch, Pestel C. FASD and the Juvenile Justice System, Diagnosis and Interventions. National Conference of Forensic Psychiatrists, Perth, Australia. 2013

Raewyn Mutch, National Youth Health Conference, Perth November 2013

Raewyn Mutch, The 4th Transcultural Mental Health and 2nd Refugee Health Conference, Perth, Western Australia from 31 October to 1 November, 2013

Raewyn Mutch, Generation Next: The Mental Health and Wellbeing of Young People. FASD, Brisbane and Perth

Raewyn Mutch, Maternal and Child Health, Global Health Short Course, InterHealth Committee, WAMSS, UWA

Melissa O'Donnell, Entering and leaving out of home care during childhood: Cumulative incidence study of groups most at risk. Developing a Data Linkage System to Enable Innovative Research Conference, Social Science Research Center (WZB) Berlin, Germany, September 2013

Carrington Shepherd, Student attendance and educational outcomes: every day counts. Department of Education, Employment and Workplace Relations, Canberra. February 28 2013

Scott Sims, Entering and leaving out of home care during childhood: Cumulative incidence study of groups most at risk. Developing a Data Linkage System to Enable Innovative Research Conference, Social Science Research Center (WZB) Berlin, Germany, September 2013

Fiona Stanley, From Data to Wisdom: Exciting Possibilities for Australia. Keynote Speak, Big Data Conference, Melbourne, Australia, July 2013

Fiona Stanley, Big Data. Better Evidence Initiative Seminar Series, Department of Health and Department of Human Services Employees, Melbourne, Australia, July 2013

Cate Taylor, Child Language Research Update: Integrating clinical and public health perspectives. Workshop presented to the Australian Association of Speech and Hearing, Adelaide, South Australia. September, 2013

Cate Taylor, Chair, Innovations in practice and policy. Centre of Research Excellence in Child Language Seminar, Murdoch Childrens Research Institute, Melbourne, Victoria. March, 2013

Cate Taylor, Trajectories in language and literacy development. Lecture presented at the Department of Education and Child Development Lunchtime Lecture Series, Adelaide, South Australia. February, 2013

Cate Taylor, Trajectories in language and literacy development. Presentation to the the Department of Education and Early Child Development, Melbourne, Victoria. February, 2013

Rochelle Watkins, on behalf of the Australian FASD Collaboration. Development of recommendations for the diagnosis of FASD in Australia. Australasian Fetal Alcohol Spectrum disorders Conference: Time to learn, time to act, Brisbane QLD 19-20 November 2013

Amanda Wilkins, Webinar for midwives on FASD in infancy and early childhood, Embrace Holistic, February 2013

Amanda Wilkins, Neurodevelopmental-Behavioural Paediatrics Society Conference, Fetal Alcohol Spectrum Disorders PowerPoint with audio for website, August 2013

Amanda Wilkins, Australasian FASD Conference, Evaluation of FASD information and services for foster carers, November 2013

Amanda Wilkins, Australasian FASD pre-conference workshop, FASD and Differential Diagnosis Case Presentation, November 2013

Steve Zubrick, Student attendance and educational outcomes: every day counts. Department of Education, Employment and Workplace Relations, Canberra. February 28 2013

LOCAL

Alison Anderson, MECP2 Duplication syndrome, Disability Services Commission, Perth, March, 2013

Eve Blair, Birth defects and growth restriction in term and late preterm singleton CP. NIH summit on Neonatal Encephalopathy and Hypoxic Ischemic Encephalopathy: Advancing the science and improving outcomes. Bethesda, May 2013

Eve Blair, Epidemiology of CP. NIH summit on Neonatal Encephalopathy and Hypoxic Ischemic Encephalopathy: Advancing the science and improving outcomes. Bethesda, May 2013

Eve Blair, Antecedents of growth restriction associated with cerebral palsy and perinatal death. Neuroepidemiology Interest Group meeting April 2013

Eve Blair, Cerebral palsy: prospects for cure and prospects for prevention. PMH Dept of Paediatric Rehabilitation Journal club. April 2013

Eve Blair, Cerebral palsy in term and late preterm

births: prospects for cure and prospects for prevention. TICHR seminar series. March 2013

Carol Bower, FASD Update. Focus on FASD Forum, March 2013

Carol Bower, Youth with FASD in the Justice System. Research Communication Forum, May 2013

Sally Brinkman, AEDI 2012 Embargoed Results. Invited Presentation to the Executive Directors. Department of Education and Training. Perth, Australia. March 2013

Sally Brinkman, Invited keynote plenary session. The AEDI results – what predicts it and what does it predict – implications for WA. West Australian Primary Principals Association (WAPPA) Annual Conference. Perth, West Australia. June 2013

Professor Jonathan Carapetis, Western Australian Primary Principals Association Inc. Annual Conference "Strong Foundation, Strong Future", Perth, WA.

Professor Jonathan Carapetis, Australian Society for Medical Research Week Symposium Opening, Plenary Speaker, Edith Cowan University, Mt Lawley Campus, WA.

Professor Jonathan Carapetis, Western Australian Statewide Aboriginal Health Planning Forum, Perth, WA.

Professor Jonathan Carapetis, InSPiRE Research Training Conference, The University of Western Australia, Perth, WA.

Jenny Downs, How does a severe disorder such as Rett syndrome affect girls and women and their families? HERE&NOW13 Disability and the Arts Symposium, Lawrence Wilson Art Gallery, University of Western Australia, Perth, August 2013

Jenny Downs, Rett syndrome, health and participation, Leadership and Professional Development Day, Disability Services Commission, Perth, March 2013

Brad Farrant, Climate change, child health and wellbeing. WA Early Childhood Education and Care Pre-Conference Research Symposium, 25 October 2013, Perth, Australia

Noula Gibson, Differentiation and Quantification of Hypertonia and the (reliable) Cerebral Palsy Description form. WA Health Child Development Centre, January 2013

Rebecca Glauert, Linking data to build and evidence base- The WA Developmental Pathways project. Child Australia Conference, ECU. Perth, October 2013

Rebecca Glauert, Linking data to build and evidence base- The WA Developmental Pathways project. WA Department of Treasury. Perth, September, 2013

Rebecca Glauert, Children in your community. Mount Barker Shire, Western Australia. April, 2013

Kirsten Hancock, Student attendance and educational outcomes: every day counts. Keynote presentation to the Western Australian Department of Education Conference of Low SES Schools. Fremantle, 1 November 2013

Kirsten Hancock, Student attendance and educational outcomes: every day counts. Western Australian Department of Education, East Perth, WA. 15 March 2013

Heather Jones, Alcohol and Pregnancy and FASD Research Update. Focus on FASD Prevention, May 2013

Heather Jones, UWA Law Students. FASD and implications for justice system. 28 August 2013

Heather Jones, WA Department of the Attorney General Heads of Jurisdiction Meeting. 5 August 2013

Heather Jones, FASD and the Justice System. Childrens Court Magistrates. March 2013

David Lawrence, Student attendance and educational outcomes: every day counts. Western Australian Department of Education, East Perth, WA. 15 March 2013

Helen Leonard, Progress in the understanding of the rare disorder, Rett syndrome-two decades of research from Western Australia. Human Genetics Society of Australasia (Western Australian Branch), Perth, May, 2013

Helen Leonard, Using epidemiology to understand the determinants of intellectual disability disorders and their outcomes for affected children and their families. Disability and the Arts Symposium, Perth, August 2013

Raewyn Mutch, FASD and the Justice System. Childrens Court Magistrates. March 2013

Raewyn Mutch, FASD consideration and diagnosis and care. Staff development day, Southwell Child Development Services, including medical and allied health staff. 2013

Raewyn Mutch, WA Department of the Attorney General Heads of Jurisdiction Meeting. 5 August 2013

Raewyn Mutch, Aboriginal Legal Service State Conference. Recognising FASD

Raewyn Mutch, Aboriginal Legal Service state wide interactive teaching to legal staff to review methods to recognise and consider FASD

Raewyn Mutch, Princess Margaret Hospital for Children, Research and Advances, FASD among refugee children

Melissa O'Donnell, Supervision and Mentoring: Managing the relationship. Centre for Research Excellence in Aboriginal Health and Wellbeing Student Day, Perth, Australia, August 2013

Jan Payne, Alcohol and Pregnancy: Midwives' knowledge, attitudes and practice. WA Country Health Service Midwifery Advisory Forum. Invited presentation, April 2013

Jan Payne, A researcher's perspective on planning consumer and community participation in research. Consumer and community participation in health and medical research: a training workshop for researchers, April 2013

Carrington Shepherd, Student attendance and educational outcomes: every day counts. Western Australian Department of Education, East Perth, WA. 15 March 2013

Scott Sims, Children in your community. Mount Barker Shire, Western Australia. April, 2013

Andrew Whitehouse, Keynote Speaker, WA Community Health Nurse Annual Conference

Andrew Whitehouse, Keynote Speaker, Population Health Postgraduate Student Research Symposium

Steve Zubrick, Student attendance and educational outcomes: every day counts. Keynote presentation to the Western Australian

Department of Education Conference of Low SES Schools. Fremantle, 1 November 2013

Steve Zubrick, Student attendance and educational outcomes: every day counts. Western Australian Department of Education, East Perth, WA. 15 March 2013

Active collaborations

BIRTH DEFECTS

Michele Hansen

Dr Georgina Chambers, National Perinatal Epidemiology and Statistics Unit, UNSW, NSW

Heather Jones

National Organisation for Fetal Alcohol Spectrum Disorders Australia. Australian & New Zealand FASD Practice Consortium 2013-2014

Joint collaboration. Alcohol & Pregnancy & FASD Research Group, Telethon Kids Institute/ Western Australian Drug and Alcohol Office 2012-2014

Jan Payne

Injury Control Council of Western Australia, Alcohol and Pregnancy Peer Educator Project, Steering Group 2013-2014

Advisor Foundation for Alcohol Research and Education, What women want to know project

Gavin Pereira

Yale University USA: Michelle L. Bell, Kathleen Belanger, Keita Ebisu, Giuseppe Amatulli

Harvard University USA: Hyung Joo Lee, Petros Koutrakis

University of Rochester USA: David Rich

Ottawa Hospital Canada: Fatima Haggar

Melbourne University: Billie Giles-Corti, Karen Villaneuva

Rochelle Watkins

University of Sydney Lililwan Project

Advisor Foundation for Alcohol Research and Education, What women want to know project

National Organisation for Fetal Alcohol Spectrum Disorders Australia. FASD workshop for service providers

Collaboration for Applied Research and Evaluation (CARE)

Dr Brad Jongeling, Paediatrician, Child Development Service, Community and Child Health, Child and Adolescent Health Service

Craig Russell, Specialist Clinical Psychologist, Child Adolescent Mental Health Service, Child and Adolescent Health Service

Sue Kiely, Senior Coordinator Workforce Development, Community and Child Health, Child and Adolescent Health Service

Anne-Marie McHugh, State wide coordinator, Aboriginal Maternity Service Support Unit (AMSSU), Women and Newborn Health Service / Aboriginal Health Council of Western Australia

Angela O'Connor and Renate McLaurin, Drug and Alcohol Midwifes, Women and Newborns Drug and Alcohol Service, Womens and Newborns Health Service

Terri Barrett, Director Midwifery, King Edward Memorial Hospital, Womens and Newborns Health Service

Professor Yvonne Hauck, Professor of Midwifery, Curtin University, King Edward Memorial Hospital, Womens and Newborns Health Service

Anne Rae, Director Allied Health and Head: Nutrition and Dietetics, King Edward Memorial Hospital, Womens and Newborns Health Service

Professor Karen Edmund, Winthrop Professor, Aboriginal Clinical Child Health and Consultant Paediatrician, Child and Adolescent Health Service

Keren Geddes, Specialist Clinical Psychologist, Child Adolescent Mental Health Service Rockingham, Child and Adolescent Health Service

Sue Bradshaw, Principal Policy Officer, Community and Child Health, Child and Adolescent Health Service

Michelle Gray, Principal Policy Officer, Western Australian Drug and Alcohol Authority

Dr Darryl Efron, Paediatric Research Network, Murdoch Childrens Research Institute

Dr Emma Sciberras. Post Doctoral Research Fellow, Community Child Health, Population Health, Genes and Environment

Associate Professor Harriet Hiscock, Paediatrician, Centre for Community Child Health, The Royal Children's Hospital Leader, Healthcare Innovation Affinity Group, Murdoch Childrens Research Institute, Principal Fellow, Department of Paediatrics, The University of Melbourne

Dr Angela Luangrath, Senior Fellow, Centre for Community Child Health, Royal Children's Hospital

Professor Ric Fordham, Economist, East Anglia University

Emeritus Professor Louis I Landau, Principal Medical Advisor, Medical Workforce, Department of Health

INFECTIOUS DISEASES

David Smith, PathWest Laboratory Medicine, Perth WA

Anthony Keil, Department of Microbiology, Princess Margaret Hospital, Perth WA

Anne Mahony, Population Health, WA Country Health Services – Goldfields WA

Bega Garnbirringu Health Services , Kalgoorlie WA

Harvey Coates and Francis Lannigan, ENT Specialists, Princess Margaret Hospital for Children, Perth WA

Christine Jeffries-Stokes, Annette Stokes The Rural Clinical School of WA, Kalgoorlie WA

Tom Riley , Microbiology and Immunology, The University of Western Australia, Perth WA

Amanda Leach, Heidi Smith-Vaughan, Menzies School of Health Research, Darwin NT

Dr Paul Effler, Carolien Giele Communicable Disease Control Directorate, Department of Health, Perth WA

Ngunytju Tjitji Pirni Inc, Kalgoorlie WA

Allan Cripps, Gold Coast Campus, Griffith University, Qld

Peter Siba , William Pomat, Suparat Phuanukoonnon, Papua New Guinea Institute of

Medical Research, Goroka, Papua New Guinea

Andrew Greenhill, Monash University Gippsland Campus, Vic

Eileen Dunne, Catherine Satzke, Murdoch Children's Research Institute, Melbourne, Victoria

Anita H. J. van den Biggelaar, Crucell, The Netherlands

Trevor Duke, Centre for International Health, University of Melbourne

Megan Passey, University Centre for Rural Health-North Coast, University of Sydney

Heath Kelly, Epidemiology Unit, Victorian Infectious Diseases Reference Laboratory, Melbourne, Victoria

Professor Geoff Shellam, School of Pathology and Laboratory Medicine, University of Western Australia, Perth, WA

Associate Professor Geoff Mercer and Dr Katie Glass, National Centre for Epidemiology and Population Health, Australian National University, ACT

Drs Heather Gidding and Bette Liu, School of Public Health & Community Medicine, University of New South Wales, NSW

Professor Peter McIntyre, National Centre for Immunisation Research and Surveillance, NSW

Professor Heath Kelly, Victorian Infectious Diseases Reference Laboratory, VIC

Professor David Burgner, Murdoch Children's Research Institute, VIC

The Global Influenza Vaccine effectiveness (GIVE) collaboration

Allen Cheng and the FluCAN Network

University of Western Australia, Perth WA

Murdoch Childrens Research Institute, Melbourne, WA

Menzies School of Health Research, Darwin, NT

Charles Darwin University, NT

Walter & Eliza Hall Institute , Melbourne, VIC

Medicines Development Limited, Melbourne, VIC

Monash Institute of Pharmaceutical Sciences, Melbourne, VIC

Centre of International Child Health, Melbourne, VIC

University of New South Wales, Sydney, NSW

University of Auckland, Auckland, NZ

University of Cape Town, Cape Town, South Africa

World Heart Federation, Geneva, Switzerland

Institute for Health Metrics and Evaluation, Seattle, USA

University of Tennessee Health Science Centre, Memphis, USA

INTELLECTUAL DISABILITIES

Dr Gordon Baikie, Royal Children's Hospital, Melbourne.

Dr Xinhua Bao, Department of Paediatrics and Obstetrics, Peking University First Hospital, Beijing, China.

Dr Michaeline Bresnahan, Columbia University, New York, USA.

Dr Julie Briody, Department of Nuclear Medicine, The Children's Hospital at Westmead, Sydney.

David Burgner, Murdoch Children's Research Institute, VIC 3052 Australia.

Dr Ron Chalmers, Disability Services Commission WA, Directors General Steering Committee, Developmental Pathways Project, TICHR.

Prof John Christodoulou, Children's Hospital, Westmead, NSW.

The Children's Hospital at Westmead.

Dr Mark Davis, Royal Perth Hospital, Perth.

Dr Carolyn Ellaway, Children's Hospital, Westmead, NSW.

Prof Elizabeth Elliott, Paediatrics & Child Health, Children's Hospital, Westmead, FASD Collaboration.

Katheryn Frame, The International Foundation for CDKL5 Research, USA.

Dr Michael Freilinger, University of Vienna, Austria.

Prof Sue Fyfe, Faculty of Health Science, Curtin University, Perth.

Prof Elizabeth Geelhoed, School of Population Health, UWA.

Dr Mika Gissler, THL National Institute for Health and Welfare, Helsinki, Finland.

Dr Raz Gross, Columbia University, New York, USA.

Ronnie Hagan, Department of Neonatology, School of Women's and Infants' Health, UWA, Perth.

Dr Kylie Hill, School of Physiotherapy, Curtin University, Perth.

A/Prof Mady Hornig, Columbia University, New York, USA

Institute of Psychiatry, London, UK.

Julie Ireland, Down Syndrome WA

Biostatistics, Karolinska Institutet, Stockholm, Sweden.

Prof Walter Kaufmann (for the RettSearch Consortium), Professor of Neurology, Harvard Medical School, Boston Children's Hospital, Boston, USA

Boston, MA 02115 Gwynnyth Llewellyn, University of Sydney, Sydney.

Prof Nick Lennox, University of Queensland, Queensland.

Dr Meir Lotan, Israeli Rett Centre, Tel Aviv, Israel.

Prof Vera Morgan, University of Western Australia.

Dr Lakshmi Nagarajan, Department of Neurology, Princess Margaret Hospital, Perth.

Norwegian Institute of Public Health, Oslo, Norway.

A/Prof Anastasia Iliadou Nyman, Department of Medical Epidemiology and

Dr Eric Parner, University of Aarhus, Denmark.

Dr Alan Percy, University of Alabama, USA.

Dr Mercè Pineda, Centro Médico Teknon and Sant Joan de Déu Hospital, Barcelona, Spain.

Dr Rohit Pokharel, Muscular Dystrophy

Foundation, Kathmandu, Nepal.

Dr Manuel Posada, National Institute for Rare Diseases Research, Madrid, Spain

Dr Abraham Reichenberg, Institute of Psychiatry, London,UK

Dr Gabriel Ronen, McMaster University, Canada.

Dr David Roye, Morgan Stanley Children's Hospital of New York, New York, USA.

Prof Linda Slack-Smith, School of Dentistry, Oral Health Centre of Western Australia, Perth.

Sven Sandin, Karolinska Institutet, Stockholm, Sweden.

Dr Diana Schendel, National Center on Birth Defects and Developmental Disabilities, Centers for Disease.

Jackie Softly, Down Syndrome WA

Dr Camilla Stoltenberg, Norwegian Institute of Public Health, Oslo, Norway.

Dr Pal Suren, Norwegian Institute of Public Health, Oslo, Norway

Prof Ezra Susser, Columbia University, New York, USA.

Dr Andre Sourander, Turku University, Turku, Finland

Dr Teresa Temudo, Hospital Geral de Santo Antonia, Porto, Portugal.

Turku University, Turku, Finland.

Dr Michael Vitale, Morgan Stanley Children's Hospital of New York, New York, USA.

Dr Simon Williams, Department of Neurology and Padiatric Rehabilitation, Princess Margaret Hospital, Perth.

Dr Ingergerd Witt-Engerstrom, Swedish Rett Centre, Sweden.

Dr Helen Woodhead, Sydney Children's Hospital, New South Wales.

Dr Xiru Wu, Department of Paediatrics and Obstetrics, Peking University First Hospital, Beijing, China.

Dr Bruria Ben Zeev, Pediatric Neurology, Safra Pediatric Hospital, Tel Hashomer, Israel.

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Prof Valsamma Eapen, UNSW, NSW Australia

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Prof Nicole Rinehart, Deakin University, Melbourne Australia

Prof Dennis Moore, Monash University, Melbourne Australia

A/Prof Adam Guastella, University of Sydney, NSW Australia

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Prof Martha Hickey, University of Melbourne, Vic Australia

Prof Simon Fisher, Max Planck Institute, Netherlands

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Prof Kevin Durkin, University of Strathclyde, Scotland

Prof Craig Newschaffer, Drexel University, Philadelphia US

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Dr John Wray, State Child Development Centre, WA Australia

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Dr Laura Thomas, Edith Cowan University

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Prof Marni Brownell, University of Manitoba, Manitoba Centre for Health Policy, Canada

Prof Jane Fisher, The Jean Hailes Foundation, Monash University, Victoria, Australia

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Dr Daryl Higgins, Australian Institute of Family Studies, Melbourne, Australia

Dr Melissa Kaltner, Queensland Health, Brisbane, Australia

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David Engelhardt, Department for Education and Child Development, South Australia, Australia

Dr Sharon Goldfeld, Royal Children's Hospital Centre for Community Child Health, Melbourne, Australia

Dr Amer Hasan, World Bank Indonesia, Jakarta, Indonesia

Professor Menno Pradhan, VU University, Amsterdam, The Netherlands

Professor John Lynch, The University of Adelaide, Australia

Associate Professor Magdalena Janus, McMaster University, Hamilton, Canada

Associate Professor Kimberley Schonert-Reichl and Assistant Professor Martin Guhn, University of British Columbia, Vancouver, Canada

Professor Sven Silburn, Menzies School of Health Research, Northern Territory, Australia

Professor Vaughan Carr, University of New South Wales, Australia

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Linda Harrison, Charles Sturt University, Bathurst.

Ben Edwards, Australian Institute of Family Studies.

Sybille McKeown, Glen Draper, Brent Bufton (Australian Bureau of Statistics), Geoff Davis & Di Rosman (WA Department of Health), and Daniel McAullay (Aboriginal Health Council of WA).

Fabrizio D'Esposito, Amanda Cooklin, (Parenting Research Centre) Rebecca Giallo (Murdoch Childrens Research Institute), and Jan M. Nicholson (La Trobe).

Sandra Eades (University of Sydney), and Bridgette McNamara and Lina Gubhaju (Baker IDI Heart and Diabetes Institute).

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Rachel Skinner, University of Sydney.

David Burgner, Murdoch Childrens Research Institute.

Fiona Armstrong, Climate and Health Alliance, Victoria.

Professor Maurice B. Mittelmark, University of Bergen, Norway

Steve Kisely, The University of Queensland

Philip Hull, Cancer Council New South Wales

Paco Perales Perez, Angela Higginson, Janeen Baxter, Mark Western, Bernard Baffour, and Michele Haynes, The University of Queensland

Matt Sanders, The University of Queensland

Lorraine Mazzerolle, The University of Queensland

Colm Harmon, The University of Sydney

Deborah Cobb-Clark, The University of Melbourne

Therese O'Sullivan, Edith Cowan University

LOOKING AT LANGUAGE

Prof Mabel Rice, University of Kansas. USA

Professor Shelley, University of Nebraska Medical Center, USA

Dr Javier Gayan, Bioinfosol, Spain.

RAINE

University / Institute, Department, City, Country

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Bradford Institute for Health Research, Born in Bradford Cohort, Bradford, United Kingdom

Bristol University, Avon Longitudinal Study of Parents and Children (ALSPAC), Bristol, United Kingdom

Cardiff University, Cardiff, United Kingdom

Columbia University, College of Physicians and Surgeons, New York, United States

Curtin University of Technology, Perth, Australia

Durham University, Durham, United Kingdom

Elsie Widdowson Laboratory, MRC Collaborative Centre for Human Nutrition Research, Cambridge, United Kingdom

Erasmus Medical Center, Generation R Cohort, Rotterdam, The Netherlands

Federal University of Pelotas, Pelotas Cohort, Pelotas, Brazil

Flinders University, Nutrition and Dietetics, School of Medicine, Adelaide, Australia

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Orebro University, Orebro, Sweden

Queensland Institute for Medical Research, Brisbane, Australia

Singapore Institute for Clinical Sciences, Genome Institute of Singapore, , Singapore

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The Murdoch Childrens Research Institute, Melbourne, Australia

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University of Sydney, Brain & Mind Research Institute, Sydney, Australia

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University of Adelaide, Adelaide, Australia

University of Albany, Albany, Australia

University of Auckland, Auckland, New Zealand

University of Bristol, Bristol, United Kingdom

University of Copenhagen, Danish Birth Cohort, Copenhagen, Denmark

University of Edinburgh, Edinburgh, United Kingdom

University of Exeter, Exeter Family Study, Exeter, United Kingdom

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University of Melbourne, The Royal Women's Hospital, Melbourne, Australia

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University of Otago, Christchurch, New Zealand

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University of Queensland, Queensland Institute of Medical Research Institute, Brisbane, Australia

University of South Australia, Adelaide, Australia

University of Southamptom, Southampton Womens cohort, , United Kingdom

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RAINE – NUTRITION

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PUBLICATIONS

1. Astfalck RG, O'Sullivan PB, Smith AJ, Straker LM, Burnett AF. Lumbar spine repositioning sense in adolescents with and without non-specific chronic low back pain - An analysis based on sub-classification and spinal regions. Manual Therapy. 2013;18(5):410-7. http://www.scopus.com/inward/record.url?eid=2-s2.0-84883307113&partnerID=40&md5=0a39d5cce62db10cf10d3bfafeb9e3f5

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SCHOOL OF PAEDIATRICS AND CHILD HEALTH

Overview

Our group's current key research focuses on:

- mechanisms involved in acute respiratory virus infections in early life, and how these affect the immune system, airway microbiome and the later development of asthma
- asthma in children: viruses, immunology and microbiome – team has discovered that human rhinovirus group C is: main cause of severe children's asthma; causes majority of acute attacks; most common cause of wheeze in < 2yr olds; only respiratory virus related to atopy
- immunogenetics: asthma, allergy, HIV (Gates grant - Africa), early respiratory infections (Africa)
- epigenetics: Finland/Russia, Greenland/ Denmark Inuits, maternal in utero contribution to infant

Our most interesting findings to date are that human rhinovirus (HRV) infection occurs in around 85% of acute attacks of asthma in children and that HRV species C (HRV-C), the newly discovered HRV species, is found in around 60% of all cases (Bizzintino *et al.* ERJ 2011). In addition, we have just shown that children who have had acute asthma caused by HRV-C are more likely to have a further hospital admission than children whose asthma was caused by another HRV species or another virus (Cox *et al.* AJRCCM 2013). Most interesting of all, our latest analysis shows that children with acute asthma caused by HRV-C infection have significant increases in serum IgE levels (both total and specific) during the acute attack (manuscript in preparation). Furthermore, this increase is confined to children infected with human rhinovirus (HRV-C).

In summary, HRV-C:

- causes over half the cases of acute severed asthma in children
- causes more severe asthma attacks than other viral species
- causes increases in IgE levels during the acute asthma exacerbation
- is associated with increased re-admissions for acute asthma over the following months

MAVRIC

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In recent years, human rhinovirus (HRV) infection, particulary the newly-identified HRV group C (HRV-C), has been recognised as the cause of the majority of acute wheezing episodes in young children. Considerable evidence suggests that HRV-C is more pathogenic in this age group than other HRV groups and viruses.

Main Aim: To determine factors related to host susceptibility to HRV-C and to ascertain specific short and long-term responses to HRV-C infection.

Main Hypothesis: Young children who develop severe wheezing with HRV-C infection have significant impairment of crucial components of their innate and adaptive immune responses to HRV-C and have adverse short and long-term responses to HRV-C infection.

Specific Hypotheses: Young children who develop acute wheezing due to HRV-C have:

1. Impairment of the interferon (IFN) response to HRV-C, as evidenced by a reduction in upregulation of IFN-related gene networks that are connected by IRF7.
2. Impaired ability to generate effective antibodies to HRV-C.
3. Disruption to their airway microbiome.
4. A distinctive clinical pattern of recurrent infections and wheezing episodes due to HRV-C.

This project was funded the National Health and Medical Research Council

PERTH RESPIRATORY BIRTH COHORT (PRBC), PREVIOUSLY KNOWN AS THE OSBORNE PARK COHORT

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The Perth Respiratory Birth Cohort (PRBC) study is one of the most prominent and comprehensive respiratory birth cohort studies to date. The cohort has many strengths including the most extensive longitudinal assessments of respiratory function from infancy into late adolescence, the only longitudinal assessments of airway responsiveness (AR) from birth through childhood and a major analysis of immunological function in mid-childhood. It also has more detailed early pulmonary function measurements and a tightly controlled early protocol. Beginning in 1987, 253 unselected subjects were recruited before birth, studied soon after birth and followed up with comprehensive, well-characterised, face-to-face reviews on seven occasions over 24 years. To summarise, findings made on the cohort to date include establishing:

- that infant respiratory function tracks through childhood and predicts wheeze and asthma
- the pattern of airway responsiveness through childhood and the factors that influence this
- relationships between early immunological responses and immunological and respiratory outcomes through childhood
- key relationships between immune system responses, cytokine regulation and respiratory status
- the nature of age-related genetic associations with atopy and asthma

Findings to date have resulted in 63 publications, 10 book chapters, consistent international prominence and numerous invited presentations at major international scientific meetings. The proposed study aims to extend these findings into early adulthood. Doing this will allow an examination of how early risk factors influence respiratory and immunological status in adulthood. The findings have important implications to our knowledge of whether risk factors that adversely affect children's respiratory status are the antecedents of respiratory ill health in adults.

This project was funded by the National Health and Medical Research Council and Princess Margaret Hospital Foundation Seeding Grant

RELAX

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A phase-3, multi-centre, double blind, randomised, placebo0controlled, study testing the efficacy of winter only treatment with omalizumab for the reduction of asthma exacerbations in children aged 6-15. Primary endpoint: proportion of children with acute asthma exacerbations during treatment period. Secondary: 1) The proportion of viral respiratory infections that result in lower airway symptoms during the treatment period; 2) lung function and airway responsiveness over the follow-up period. Mechanistic: 1) aeroallergen specific IgE titres over the follow-up period; 2) Allergen-specific Th2 memory responses over the follow-up period; 3) the circulating pool of FcER1+ myeloid cells; 4) gene activation signatures on circulating myeloid cells during acute exacerbation; 5) presence of virus and interactions between virus and bacteria. Safety: urticaria or anaphylaxis to omalizumab, treatment-related adverse events, haematology and clinical chemistry.

This project is funded by the National Health and Medical Research Council

CYSTIC FIBROSIS GLUTATHIONE GENETICS

Dr Ingrid Laing (School of Pediatrics and Child Health) and AREST CF

To identify the glutathione pathway gene variations that alter lung glutathione levels and begin to elucidate the initiation of lung disease in CF. This knowledge will facilitate the identification of therapeutic intervention targets prior to the establishment of respiratory infection, with treatments targeted to those most likely to be affected and to the most relevant tissue compartment, in an effort to slow the development of respiratory OS and inflammation, reduce airway damage and delay the onset of bronchiectasis.

This project is funded by the University of Western Australia

INFECTIONS IN AFRICAN POPULATIONS

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This project is comprised of case-control and cross-sectional studies from three distinct populations in Africa (Mozambique, South Africa and Morocco). The key aims of this project are to identify the viruses and bacteria associated with acute lower respiratory infections (ALRI) and to investigate the host immune responses (i.e. cytokine and antibody responses) associated with respiratory infections in young African children. The results of this project will elucidate the role of viruses, bacteria and host immunity in childhood ALRI and may therefore contribute to preventative and clinical strategies as well as lead to further biomarker discovery studies.

This Project was funded by the Lung Institute of Western Australia, Alan King Westcare Project Grant

GAMA

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Le Souëf's group component: Development of novel biomarkers distinguishing early HIV infection from longstanding infection in a Sub Saharan African setting.

Aims: 1) Conduct microarray for host gene expression of cytokine,chemokine and IBD GI biomarkers; 2) Analyze individual biomarkers for their mean duration of recency from the longitudinal cohort, and determine false recent rate from the longstanding HIV infected patients; 3) Analyze combinations of biomarkers for best distinguishing recent from longstanding HIV infection.

This project was funded by the Bill and Melinda Gates Foundation

GENOME-WIDE DNA METHYLATION IN CHINESE IMMIGRANTS

[1]Dr Guicheng Zhang, [1]Prof Peter Le Souef, [2]Dr Siew-Kim Khoo, [2]Mrs En-nee Schultz, [2]Assoc Prof Belinda Hales, [1]Prof Jack Goldblatt

[1]School of Pediatrics and Child Health, [2]Telethon Institute for Child Health Research

Prevalence of asthma and allergy is consistently higher in Western countries such as Australia than in developing countries such as China. After their arrival in Australia, Chinese immigrants have a gradual increase in prevalence of asthma and allergy to the same level as in the local population or even higher [*Respirology*. 1996; 1: 123-126. *Med J Aust 1994*;161:418-425]. This increase in prevalence of asthma and allergy in immigrants may be

related to abrupt environmental changes related to housing and domestic environments, Western diet and lifestyles that the immigrants encounter after moving from an asthma low-risk environment (China) to a high-risk region (Australia). Methylation, which is an environmentally induced epigenetic code, is a central epigenetic modification that has essential roles in cellular processes including genome regulation, development and disease. We, therefore, hypothesize that the abrupt environmental changes that Chinese immigrants experience would have re-shaped their whole-genome methylation profile, thereby contributing to the increased asthma and allergy in them.

This project is funded by the Telethon Institute for Child Health Research

GENOME-WIDE DNA METHYLATION PROFILING IN CHILDREN WITH ACUTE ASTHMA AND HRV-C INFECTION

[1]Dr Guicheng Zhang, [1]Prof Peter Le Souef, [2]Dr Siew-Kim Khoo, [2]Mrs En-nee Schultz, [1]Prof Jack Goldblatt, [1]Dr Joelene Bizzintino

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We recently found that human rhinovirus group C (HRV-C) was the most common viral group causing severe acute wheezing episodes, and half of the acute wheezing attacks, in young children. More importantly, we found that HRV-C was the only respiratory virus that was associated with atopy (defined by skin prick tests), total and specific IgE in an acute asthma cohort, suggesting that HRV-C may be the key to asthma exacerbations and the development of allergy and asthma in children. Our team, together with Prof Patrick Holt in Cell Biology at the Telethon Institute for Child Health Research, have investigated the gene expression profile of peripheral blood mononuclear cells (PBMC) using a genomics-based approach in the acute asthma cohort. Methylation, which is a persistent, but also reversible epigenetic code, has central epigenetic roles in cellular processes including genome regulation, gene expression and development and disease. We propose to investigate genome-wide methylation patterns of PBMC in children with acute asthma associated with HRV-C, compared to methylation profiles of the same subjects in convalescence, to children with acute asthma associated with HRV-A and in healthy children without HRV and other respiratory virus infections. The study is timely to explore an epigenetic explanation to the role of HRV-C in asthma exacerbations and the development of asthma and allergy in children. In order to cover a wider spectrum of genes in the whole genome, this proposed project will use an Illumina 450k Infinium Methylation BeadChip (Infinium Methylation 450K; Illumina, Inc. CA, USA). The Infinium 450K includes 485,577 assays (482,421 CpG sites, 3091 non-CpG sites and 65 random SNPs). The array covers a total of 21,231 genes with a global average of 17.2 sites per gene region. This study will comprehensively investigate the methylation changes in relation to infection with different HRV strains in children with acute asthma recruited at the Princess Margaret Hospital for children (PMH). Dr Zhang, the chief applicant has a solid background in both genetic and epigenetic aspects of asthma and allergy and biostatistics. He will use a gene co-expression network analysis algorithm to investigate co-methylation networks in the response to HRV-C infection in children with acute asthma. The study will increase our understanding of the mechanisms underlying asthma exacerbations and the development of allergic disorders and asthma in relation to HRV infection. The findings should facilitate designing and testing of new preventive strategies or therapeutic interventions (targeting methylation profiles) in Australia, where asthma is a significant social burden.

This project was funded by the Princess Margaret Hospital Foundation.

Staff and Students

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William Cookson (MD)

Holly Clifford (BSc. Hons., PhD)

THESES PASSED

Aarti Sainganesh (Hons. W.Aust.)

Allergic symptoms and immune responses in Chinese immigrants living in a Western environment

Leesa Harris (Hons. W.Aust.)

Contribution of MNDA gene variation to wheezing attacks and response to treatment

Cassie Robertson (Hons. W.Aust.)

Recurrence of Human Rhinovirus Group C in children that suffer multiple wheezing attacks

Hasmita Patel (Hons. W.Aust.)

Are endotoxin and House Dust Mite (HDM) allergens levels responsible for development of allergic diseases in the Peel region?

Erica Parker (Hons. W.Aust.)

The relationship between viral load at presentation with acute HIV infection and clinical outcomes in the early stages of disease

Awards

Alicia Annamalay, Asthma Foundation PhD Top-up Scholarship

Alicia Annamalay, Convocation Award by UWA Postgraduate Research School

Alicia Annamalay, UWA Postgraduate Travel Award

Stephen Oo, Telethon Research Fellowship Scholarship

Stephen Oo, American Thoracic Society Abstract Scholarship Award

Louisa Owens, UWA International Postgraduate Research Fellowship

External Committees

INTERNATIONAL

Peter Le Souef

Member, Pediatric Advisory Board

INTERASMA

Chair

WAO Special Committee on Pediatric Asthma

World Allergy Organization

NATIONAL

Peter Le Souef

Councillor, AMA and AFWA representative

Australian Council on Smoking and Health, 2004–present

LOCAL

Invited Presentations

Peter Le Souef

Overview of aerosol devices and therapy today. Workshop: State-of-the-Art in Aerosol Therapy

Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Darwin

The role of respiratory viruses in children's asthma, National Forum on Pediatric Asthma and Allergy, Beijing, China

Asthma control in China, National Forum on Pediatric Asthma and Allergy, Beijing, China

Are inhaled steroids helpful in infants with recurrent wheeze?: Symposium: Treatment and outcome of preschool wheeze, European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization, World Allergy and Asthma Congress 2013, Milan

Allergy and asthma: Symposium: Year in review – asthma, European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization, World Allergy and Asthma Congress 2013 Milan

Virus and asthma: the starter or the main cause?, Plenary lecture: Asia Pacific Association of Pediatric Allergy, Respiratory and Immunology (APAPARI), Bangkok

The science of aerosol medications: Symposium, Asia Pacific Association of Pediatric Allergy, Respiratory and Immunology (APAPARI), Bangkok

Maintenance inhaled-steroids should be used in preschool wheezers? Con in Pro-Con Symposium

Asia Pacific Association of Pediatric Allergy, Respiratory and Immunology (APAPARI), Bangkok

The revolution in diagnostic lung imaging - changing how we practice, Symposium II: Pulmonology

Hong Kong Society of Paediatric Respirology, Hong Kong

Triggers for acute asthma – which causes what, when and why?: Plenary lecture - Symposium III

Hong Kong Society of Paediatric Respirology, Hong Kong

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