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SCIENTIFIC SUPPLEMENT





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Aetiology and pathogenesis of atopy and asthma in children

The role of bacterial infections during infancy in asthma development

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Respiratory viral infections during infancy, particularly against a background of early allergic sensitization, have been implicated as risk factors for asthma development. Recent findings suggest that bacterial pathogens may also contribute to pathogenesis but definitive data are lacking. We have addressed this question in our Childhood Asthma (CAS) birth cohort study, as part of which we have characterized the nasopharyngeal microbiome (NPM) in

the children across the first year of life, employing 16S rRNA deep sequencing. The resultant data base of >193 million sequence reads was utilized in characterizing dynamic changes in the NPM associated with viral infections, and linking these with asthma risk at 5 and 10yrs. Salient findings include: (i) the steady state NPM is dominated by commensals *Corynebacterium*, *Staphylococcus*, and/or *Alloiooccus* sp. which are largely supplanted by the pathogens *Haemophilus*, *Streptococcus* and/or *Moraxella* sp. during viral infection; (ii) the same pathogens are selected for by day-care and antibiotic treatment; (iii) rhinovirus (HRV) and RSV are independently associated with symptoms during acute respiratory illness (ARI), but after controlling for virus, *Haemophilus*, *Streptococcus* and/or *Moraxella* remained strongly associated with ARI symptoms and with infection spread to the lower airways; (iii) these bacterial pathogens plus RSV (but not HRV) were additionally associated with febrile lower respiratory illness (fLRI), which was itself a major risk factor for asthma development across the whole cohort; (iv) HRV-C infection was associated with acute wheezing (w)LRI and with subsequent asthma development, but only in "high risk" children who displayed early aeroallergen sensitization; (v) early fLRI and wLRI operated independently and additively in promoting asthma risk; (vi) time to first LRI also appears important with earlier fLRI occurring amongst children who developed asthma; relevant to this, early colonization with

Streptococcus (which was again more common in the sensitized group) was strongly associated with both earlier first LRI, and risk for subsequent asthma. We conclude that dynamic changes in the constituents of the infant NPM contribute independently to driving asthma development, and also play key modulatory role(s) in the parallel asthma causal pathway driven by interactions between virus-driven and allergen-driven inflammatory mechanisms. These studies are continuing into 2015, during which analyses of NPM samples collected during years 2-5 in the cohort will be performed.

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

Distinguishing benign from pathologic Th2-immunity in atopic children

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The majority of school children with inflammatory airway disease(s) are sensitized to aeroallergen(s), and symptom frequency and intensity associates positively with IgE titres. However only a minority of sensitized/exposed children are symptomatic, suggesting that the pathogenic effects of IgE are normally attenuated by endogenous control mechanisms. We hypothesized that aeroallergen-specific IgG that is co-produced with IgE, contributes significantly to this attenuation. To address this question, we have pooled data from our CAS and RAINE birth cohorts from Perth, together with data from the Manchester Asthma and Allergy cohort from UK. In these three independent community cohorts we have analysed relationships between serum aeroallergen-specific IgE and IgG titres and associated immunophenotypes, and susceptibility to asthma and rhinitis.

Amongst atopic children with elevated aeroallergen-specific IgE, levels of corresponding specific (total) IgG or IgG1 (and hence IgG:IgE ratios) were inversely related to the presence, severity and persistence of airway symptoms, responsiveness to intradermal allergen challenge, and the potency of their sera in basophil triggering in vitro. Genome wide expression profiling of underlying aeroallergen-specific Th-memory responses revealed strong positive associations between IgG:IgE ratios and IL-10-dependent (regulatory) gene signatures, and the converse for Th2-effector signatures.

These findings suggest that following sensitization, aeroallergen-specific Th-memory matures over time driven by ongoing environmental exposure. The balance that develops between effector and regulatory mechanisms controlling the strength of the immediate (IgE-mediated) and ensuing late phase (T-cell-mediated) reactions collectively determine resistance/susceptibility to aeroallergen-induced airway symptoms. Allergen-specific IgG1, production of which is likely driven via IL-10, plays a hitherto unsuspected “gatekeeper” role in this process via limiting the intensity of the acute phase response that initiates the atopic inflammatory cascade. These findings in atopic children have implications for design of prognostic and immunotherapeutic strategies for controlling airway disease development/progression.

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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We tracked vitamin D levels from birth to age 10y in over 100 CAS cohort members; we used a highly specific, internationally-standardised method developed by Metabolomics Australia (University of Western Australia) to measure the storage form of vitamin D (25(OH)D) from cryobanked CAS plasma samples collected at birth (cord blood), 6 months and 1, 2, 3, 4, 5, & 10 years. Our findings suggest that low 25(OH)D in infancy is linked to higher numbers of severe respiratory infections up to age 5 years. We have also observed that children with low vitamin D at a high proportion of the 8 follow-up ages had increased risk of asthma, allergy and eczema at age 10y, suggesting a continuing requirement for adequate vitamin D beyond infancy and throughout childhood.

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

Prediction of asthma in childhood from wheezing phenotypes up to age 3 years: findings from the Western Australian Pregnancy Cohort (Raine Study).

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Increased number of wheezing episodes by age 3 years (with or without a cold) was associated with increased risk of asthma at age 14 years in the Raine cohort. Measures of lung function and airway calibre were reduced in 14-year-olds who had ever wheezed by age 3 (with or without a cold) compared to those who had not. Furthermore, a higher number of episodes of wheezing with a cold by age 3 predicted poorer lung function at age 14; there was no such association for wheezing without a cold, suggesting that it is increased respiratory infections rather than wheezing alone that is likely to have a persistent detrimental effect on lung function. These analyses are ongoing.

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

Uncovering the immunological mechanisms determining whether asthma waxes or wanes between adolescence and adulthood.

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Late onset and persistent (early onset) asthma in young adults are generally recognised as distinct phenotypes that are likely to be driven by different mechanisms; they are therefore likely to need different treatments, but underlying details are sparse. We have recently received funding to address these important issues within the Western Australian Pregnancy Cohort (Raine Study). A follow-up examining the respiratory health of ~1000 22-year-old Raine Study participants has recently been completed, complementing a similar follow-up that took place at age 14 years. In addition to collecting clinical data relating to asthma, both follow-ups created an archive of viable immune cell samples (peripheral blood mononuclear cells) that were collected from subjects at the time of clinical assessment, at both 14 and 23 years. This enables us to strategically examine immune function at both ages to identify immunological markers associated with remitting asthma, persistent asthma, and late-onset asthma.

This study will commence early in 2015 and is funded by the National Health and Medical Research Council of Australia.

Developmental-associated dysregulation of innate anti-microbial immunity in early life as a determinant of susceptibility to

atopic asthma

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We have established previously that children most likely to develop persistent asthma are those who experienced repeated/intense lower respiratory tract infections (LRIs) during infancy, especially if they also show early signs of atopy. The marker for asthma risk in these children was associated with the severity of the accompanying inflammation-associated respiratory symptoms, suggesting that their antimicrobial responses are dysregulated to the extent that they contribute directly to airway tissue damage. Findings in the Childhood Asthma Study (CAS) birth cohort indicate that the most asthmagenic infant LRIs are those associated with fever, a classical marker of acute inflammation and a specific marker of the underlying activation of the inflammasome complex, which mediates production of the active form of the fever-inducing cytokine, IL-1 .

We postulate that children at maximum risk of developing persistent asthma are those in whom postnatal maturation of innate immune functions are developmentally delayed, leading to transient dysregulation of their antimicrobial defence mechanisms during infancy. This project focuses on cell populations within the innate arm of the immune system that mediate initial defence against respiratory

pathogens and includes detailed assessment of inflammasome-associated functions resulting in secretion of pro-inflammatory cytokines. Using cryobanked peripheral blood mononuclear cells (PBMCs) from the CAS cohort to address this hypothesis, we examined age-associated changes in regulation of inflammasome-associated functions. One hundred and sixty cord blood samples, 166 PBMCs obtained at age 4 and 126 PBMCs at age 10 were cultured and examined for inflammatory and regulatory cytokine responses, including IL-1 following activation with innate stimuli (LPS or poly(I:C)), which we have shown to up-regulate IL-1 production and secretion. Cells from these cultures were cryobanked to measure transcriptional levels of genes associated with the inflammasome complex. A case:control subset of cord blood samples, comprising those who did not exhibit fever during an LRI against those who had multiple fevers during an LRI, was assessed by flow cytometry for caspase-1 activity, a critical component of the inflammasome complex. Analysis of these data are ongoing in 2015, which will be correlated with documented clinical outcomes in relation to asthma, particularly where individuals with an LRI showed a febrile response.

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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 little progress has been made towards the development of new treatments 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 suggested 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. In this study, we used two approaches to further our understanding of the role of IRF7 in asthma. First, siRNA technology was used to knockdown IRF7 expression in airway epithelial cells, and then the epithelial cells were infected with rhinovirus. Using microarray profiling we demonstrated that knockdown of IRF7 reduced the expression levels of genes involved in innate antiviral responses.

In the second approach, we utilized a mouse model of rhinovirus infection (attenuated mengovirus model), to determine if IRF7 regulates antiviral responses in vivo. The data showed that neutrophilic airways inflammation was increased in IRF7 knockout mice in comparison to wild type controls. Taken together, these data show that IRF7 controls the expression of innate antiviral genes and regulates airways inflammation during rhinovirus infections. These data highlight the potential utility of the IRF7 pathway to develop new treatments that modulate inflammation during asthma exacerbations.

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

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Asthma is a chronic and heterogeneous inflammatory disease that is strongly associated with sensitization to allergens, but the underlying mechanisms are poorly understood. Previous studies have largely relied on animal models or human challenge studies to elucidate the underlying mechanisms, but these approaches employ high doses of allergen, and



there is a lack of data in the context of natural allergen exposure. In this study we collected induced sputum samples from participants of the 23 year follow-up of the Raine cohort study. We hypothesized that normal domestic exposure to dust mite allergens could be leveraged to reveal asthma-associated inflammatory mechanisms via comparative profiling of the sputum transcriptome at baseline in symptomatic/asymptomatic mite sensitized subjects. The data showed that hundreds of genes were differentially expressed in house dust mite allergic subjects with or without asthma. These findings demonstrate that transcriptomic profiling of sputum-derived cells can unveil biological pathways and networks underlying the pathogenesis of asthma-related traits in the context of natural allergen exposure.

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

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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.

Epigenetic changes underpinning allergen sensitization: a twin-based study.

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Allergic diseases are one of the most common chronic inflammatory disorders afflicting humans. In genetically susceptible individuals, dysfunctional immune responses cumulatively result in the adaptive generation of IgE to specific environmental antigen(s). Defining the molecular pathways that are disrupted in IgE mediated antigen sensitization has proven to be one of the most elusive aspects



in our understanding of how to better direct approaches towards preventive or improved treatment strategies targeting allergic disease. Genetics and environmental factors alone do not independently explain development of allergic disease. Rather, allergy appears to involve a complex interplay between genetic susceptibility and environmental exposure. Recent findings suggest a role for epigenetic change, in particular DNA methylation, in the causal pathway. Using allergic asthma as an archetypal allergic disease, the central aim of this study is to identify differences in epigenetic profile specifically associated with environmentally induced allergen sensitization in humans. Recent unequivocal data in inducible mouse models of asthma have demonstrated specific disruption of DNA methylation profile in the peripheral T cell compartment. Equivalent data in humans is lacking due to the difficulties associated with teasing out the relative roles of genes and environment in the modulation of epigenetic state. An elegant approach to overcome such issues, which mirrors animal models, is to study human twins in childhood. This study aims to definitively test the link between altered DNA methylation in CD4+ T cells and allergy in genetically identical twins discordant for allergic sensitization to house dust mite. The first aim of this study is to identify methylation sensitive genes (MSG) associated with gene expression differences in monozygotic twins discordant for house dust mite (HDM) sensitization (SPT+ and SPT-)

through a within-pair comparison of the epigenetic and gene expression profiles of cells of the adaptive immune system (CD4+ T and APC cells). We have used flow cytometry to sort purify subsets of immune cells from PBMC of twin pairs and are currently in the process of examining genome wide methylation profiles. Additionally we have characterized PBMC samples to determine frequency, activation state and function of the immune cell subpopulations and are currently in the process of data analysis.

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

Finding the cellular explanation for recurrent asthma exacerbations

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SPACH***

Asthma is a complex chronic inflammatory disease affecting the airways. It develops mainly in young children and presents as several disease phenotypes of different underlying pathogenesis, severities and health care requirements. One particular subgroup of patients manifests with recurrent severe exacerbations, requiring frequent hospitalization. These patients have a high risk of developing irreversible loss of lung function and, in addition, do not

respond well to available treatments. To date, there is only limited knowledge regarding mechanisms governing recurrent exacerbations in this subset of susceptible individuals.

In this project we are testing the hypothesis that specific unique patterns of cellular and molecular inflammatory responses are associated with the recurrent severe exacerbation disease phenotype. To achieve this we are employing state of the art technology to characterize the cellular and molecular signatures of peripheral blood mononuclear cells (PBMC) collected from healthy individuals, and from patients presenting at hospital during acute asthma exacerbations across a range of exacerbation frequency scores, and in some individuals at follow-up. We are performing multi-parameter flow cytometry and transcriptome profiling (RNA-Sequencing) of PBMC samples to determine proportions of cellular subsets, activation status and corresponding gene expression. These studies will improve our current understanding of the inflammatory responses in this hard-to-treat patient group and may unveil novel therapeutic targets leading to improved treatment options for these children.

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

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Atopic asthma contributes significantly to the overall community disease burden. Sensitization to aeroallergens during early life years is a major risk factor associated with the development of atopic asthma. However of all sensitized individuals only a subset go on to develop clinically relevant airways symptoms, suggesting important roles for additional cofactors in disease pathogenesis. This study aims to map the cellular immune mechanisms that underlie expression of clinically relevant persistent forms of allergic asthma. 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 naive 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 atopic individuals: mechanistic studies in an experimental model

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Asthma is one of the most common chronic diseases in the world. Of the different pathological phenotypes associated with this disease, atopic asthma contributes most to the overall community disease burden. Sensitization to aeroallergens during early life is recognized as a potent risk factor driving development of atopic asthma in children and young adults. Sensitization to these allergens is now extremely common and occurs in half of the Australian population, however, less than 20% of at-risk sensitized subjects develop clinically relevant airways symptoms, suggesting that additional cofactors are required to drive disease pathogenesis. The role of respiratory viral infections as a cofactor contributing to allergic asthma pathogenesis, in

particular Rhinovirus (RV), is currently one of the most active areas in asthma research. It is thought that in susceptible individuals, respiratory viral infections can operate independently of atopy and/or interact synergistically with the effects of atopy to maximise asthma risk. It is additionally suggested that the atopic state may itself predispose to viral infections in the airways and this “reverse causality” may also be sufficient to explain the association. Our own investigations in this context have indicated that the connection between respiratory viral infection and atopy may be more intimate. To best compliment the findings in children showing strong associations between RV infection and acute asthma exacerbation and to mimic the essential characteristics of human disease, we have developed a model unique in the international literature. This model compares the extremes of the spectrum of susceptibility to symptomatic allergic airways disease seen in humans using rat strains expressing high (HR) versus low (LR) atopic responder phenotypes. We have examined the inflammatory response to RV 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 investigated how allergic responses interplay with existing viral infection to influence local Th2 (allergic) immune responses to aeroallergen challenge in

the airway mucosa to impact disease pathogenesis. Our findings indicate that concurrent RV infection/aeroallergen exposure results in significant worsening of airways inflammation and that genetic susceptibility and gender play important roles in the process.

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 following maternal bacterial infection

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Maternal exposure to microbial pathogens during pregnancy is frequently associated with exaggerated inflammatory responses and accompanying high intensity acute symptoms, and in some cases more profound follow-on effects ranging from the extreme of premature termination of pregnancy, to growth restriction in the offspring. Preterm birth is the single most important health care issue in fetal-maternal medicine, with a high prevalence in Australia and other developed countries. Children born with low for gestational age weight have an increased susceptibility to



subsequent development of a range of persistent diseases, exemplified by atopic asthma. Safe effective treatments that can be used to protect against infection-induced complications would provide exciting new opportunities for improving maternal, fetal and neonatal health. We have developed preclinical mouse models to study mechanisms underlying infection induced pregnancy complications. In one model we are using exposure of pregnant mice to Lipopolysaccharide (LPS), the major pathogenic component of gram-negative bacteria to induce preterm delivery, growth retardation, embryonic resorption and reduced fetal survival. 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 administration during late gestation. Our results have shown that treatment of pregnant mice with OM85BV for one week prior to LPS exposure provides significant protection against preterm birth and fetal growth retardation, potentially via modulation of immune cell populations in gestational tissues. This pre-clinical study has also demonstrated the safety of OM85BV during pregnancy and may represent a novel, safe effective treatment strategy to protect against bacterial infection-induced complications during pregnancy. The project is progressing with a detailed analysis of the cellular and molecular mechanisms associated with OM85BV mediated protection.

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

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The respiratory tract (RT) is continually exposed to a plethora of environmental antigens of pathogenic and non-pathogenic nature within inhaled air. To best maintain the crucial normal function of the respiratory tissues the respiratory immune system must constantly screen these antigens for their potential danger to the host and rapidly neutralize the threat, or alternatively must effectively ignore harmless antigens to effectively minimize unnecessary inflammation. A balanced network of antigen presenting cells (APC) play an important role in this process and are capable of regulating tolerance or immunity as required. Respiratory viral infections can pose a serious threat to immunological homeostasis in the RT via the induction of potent inflammatory and cytotoxic responses in local tissues. Disruption to the balance of immunity in the RT can

last for a prolonged period following infection, and this may potentially result in modified immune responses to other antigens during this time frame. This includes increasing the risk of allergic sensitization or decreasing resistance to secondary infections. In this study, we have used an experimental mouse model of H1N1 Influenza Type A Virus (IAV) infection in adult and juvenile animals to examine the dynamics and activation states of APC in airway mucosal (AM) and parenchymal lung (PL) tissue of the RT following a time course post IAV. We found marked differences in the selective depletion and reconstitution of dendritic cells (DC) subsets in the AM and PL environments. In adult mice, DC in the AM were shown to have a generally more acute response to infection that resolved by day 7, versus a more delayed response with persistent depletion of PL DC subsets lasting for up to 3 weeks following infection. Tissue-resident macrophages populations in the PL were also significantly altered well after viral clearance, being significantly depleted and remaining in a persistent state of activation. In juvenile mice, persistent changes in PL DC and macrophages were found for up to 5 weeks following IAV infection. These data demonstrate that IAV has differential effects on APC populations in different micro-environmental tissue compartments of the RT, leading to long-term derangement in the numbers and activation states of these cells, which likely disrupt the fine balance of immunological protection in this

environment.

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 following maternal Influenza A infection

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Following from the study above, we are also studying the impact of Influenza A infection during pregnancy on maternal and fetal health, and the potential of OM85BV to protect against complications induced by maternal respiratory viral infection. We have developed a pre-clinical mouse model that mimics human disease to study the cellular and molecular mechanisms associated with infection induced poor maternal/fetal health. In pregnant mice, clinical disease symptoms following Influenza A infection are more severe compared to non-pregnant animals, mediated in part by enhanced activation of immune cell populations in respiratory tissues. Fetal health is also compromised in infected pregnant mice with significantly reduced weights for gestational age. Pretreatment of pregnant mice with OM85BV demonstrates significant protection against clinical disease in 60% of infected pregnant mice. Furthermore,



in this subset the fetuses are protected against growth retardation. This project will progress with an investigation into the underlying cellular and molecular mechanisms associated with OM85BV mediated protection and how this impacts neonatal immune function.

This project is funded by OM PHARMA (Geneva).

Role of CD103 in the regulation of immunity to inhaled allergens

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CD103 is the α chain of integrin $\alpha E\beta 7$, 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

Leffler J, Mincham KT, Holt PG, Strickland DH

Telethon Kids Institute, The University of Western Australia, Perth Australia

Increasing rates of atopic (IgE mediated) sensitization has been identified as a key risk factor associated with the rising prevalence of allergic asthma. The nature of the immunological mechanisms that underlie generation of mucosal IgE sensitization, as opposed to the normal response of protective tolerance to aeroallergens,

remains unclear. The induction of “mucosal tolerance” to aeroallergen represents one of the established paradigms in lung immunology and involves the selective attenuation of Th2 skewed immunity, particularly production of IgE. This can be attained by repeated exposure to an allergen via the respiratory route with accompanying induction of a phenotypically heterogeneous population of T cells with “regulatory” activity. Notably, in animals with hyper-susceptibility to allergic disease and development of high IgE responses (high responder; HR) generation of mucosal tolerance required log fold higher levels of exposure to aeroallergen compared to than their low-responder (LR) counterparts. No satisfactory explanation exists to explain this profound difference in efficiency of mucosal tolerance mechanisms. Recent novel and counterintuitive epidemiological findings suggesting that risk for IgE sensitization to inhalant allergens may be inversely related to allergen exposure levels. The core hypothesis of this project is derived from these studies and our own findings that indicate 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. Our HR/LR rat model provides unique opportunities to systematically test this 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 Kids Institute, 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 Kids Institute, The University of Western Australia, Perth Australia

In common with a number of chronic diseases, a significant proportion of risk for development of potentially chronic atopic asthma is pre-set before birth, via a combination of inherited genetic factors operating in conjunction with environmental factors, which collectively impact negatively upon the health of the mother during pregnancy. These include common respiratory infections such as influenza, and atopic asthma exacerbations. It is recognised that in atopic mothers, intercurrent asthma exacerbations, in particular severe episodes, pose a significant threat to the health of the mother and to the pregnancy, exemplified through preterm delivery and fetal growth restriction leading to low birth weight babies. Maternal asthma during pregnancy has been linked to an increased likelihood of the neonate developing allergic asthma. This study uses an experimental model of allergic asthma during pregnancy to examine the mechanisms that lead to worsening maternal atopic asthma, fetal complications and increased risk of neonates to develop allergic asthma. Additionally we will investigate the therapeutic potential of an immune modulating agent (OM85BV – a bacterial extract) delivered via the gut mucosa, to protect against these pregnancy health 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. Furthermore, it is now recognized that the exacerbations in human atopy which are associated with the most severe inflammation are those triggered by concomitant exposure to viral pathogens and aeroallergens, and accordingly we are developing a pregnant mouse model to mimic this.

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

Mapping changes in immune cell populations in gestational tissues over the course of pregnancy.

Study M, Scott NM, Lauzon-Joset JF, Holt PG, Strickland DH

Telethon Kids Institute, The University of Western Australia, Perth Australia

For a successful pregnancy, the maternal immune system must make significant adaptations to tolerate the semi-allogeneic fetus. This process involves selective alterations to number, activity and function of immune cells in gestational tissues, in a tissue specific manner and dependent on gestational age. To date there remains much to be learned, but it is clear that imbalances in number and function of immune cells within gestational tissues could be critical and even fatal to the developing fetus. Maternal inflammatory responses of pathogenic and non-pathogenic origin can disturb this balance and result in adverse pregnancy outcomes

such as preterm birth and small for gestational age infants. To further our understanding of the types and roles of immune cells in gestational tissues in healthy pregnancy this study is focused on identifying the subsets of immune cells in gestational tissues (placenta, decidua, uterus, lymph nodes) and in a cross-section of other peripheral tissues over a time course of a normal healthy pregnancy. This data will serve as an invaluable guideline of normality, which will be used to better understand the mechanisms underlying pregnancy complications.

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 IFN γ and IFN α intranasal delivery on airway dendritic cells, T cells and T regulatory cells. We demonstrate the influence of IFN γ and IFN α 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

Head of Division

Patrick G Holt DSc,FAA
Telethon Kids Institute
Centre for Child Health Research, UWA

Research Staff

Dr A. Bosco , PhD - Research Fellow
Dr V. Fear - Research Fellow
Dr E.M. Hollams, PhD - Research Fellow

Mrs B.J. Holt, BSc - Research Officer

Ms A. Jones - Research Assistant

Dr D. Mok, PhD – Research Fellow

Mr R. Ng – Graduate student

Ms N Scott, B.Biomed Sci (Hons) PhD – Research Officer

Mr M. Serralha, BSc (Hons) - Research Assistant

Dr D.H. Strickland, PhD - Senior Research Fellow

*Dr P.A. Stumbles, PhD - Senior Lecturer, Murdoch University

Mrs J. Tizard - Research Assistant

Ms N. Troy – Research Assistant

*Honorary Fellow at Telethon Kids Institute; all research activities remain based within this Division.

PhD Students

Mr K. Mincham – Graduate Student (Hons)

Ms A Jones – Graduate Student

Visiting Research Fellows

Mr J Lauzon-Joset, University of Quebec, Canada

Mr J. Leffler, Lund University, Sweden

Theses Passed

Laurence Chung, PhD, University of Western Australia

External Committees

Prof Patrick Holt

Australian Academy of Science:
Sectional Committee for Medicine and
Public Health

MAAP External Advisory Board, Henry
Ford Health System, Detroit

Scientific Consultant; Christine-Kühne
Center for Allergy Research and
Education (CK-CARE), Munich

Dr Deborah Strickland

National Health and Medical Research
Council Early Career Fellowship – Panel
Member

ACS National Conference Organising
Committee Member

Invited Presentations

International

Prof Patrick Holt-Symposium Speaker:
The role of T-cell immunity in the
inception of allergy and asthma – EAACI
Congress, Copenhagen, 2014.

Symposium Speaker: Distinguishing
benign from pathological Th2 immunity
in atopic children – Collegium
Internationale Allergologicum Congress,
Petersberg, 2014.

Prof Patrick Holt-Symposium Speaker:
Update on the Origins of Asthma:
Insight from birth cohort studies –
Nemacolin Asthma Conference,
Pittsburg, 2014.

Institute of Pathology, Rikshospitalet,
Oslo, 2014 (Professor Frode Jahnsen):
Role of allergen specific IgG1 in
modulation of allergic inflammation.

Prof Patrick Holt-Respiratory Centre,
University of Arizona, Tucson, 2014
(Prof F Martinez): Distinguishing benign
versus pathological atopy in children.

National

Dr Anthony Bosco, DOHaD Society of
ANZ meeting, Perth, oral presentation,
2014.

Dr Deborah Strickland:

Oral Presentation; Society Reproductive
Biology; Melbourne.

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

Local

Dr Deborah Strickland:

Seminar Series; Curtin University
Chair, Immunology Working Group
Workshop

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: Rottneest Annual Scientific Respiratory Meeting. Using network graph theory to understand asthma.

ACTIVE collaborations

Prof Patrick Holt

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

Peter Sly, Queensland Children's Medical Research Institute, Australia

Hugh Sampson, Department of Pediatrics, Division of Allergy & Immunology, Mount Sinai School of

Medicine, USA

Steve Durham, Dept Allergy & Clinical Immunology, National Heart & Lung Institute, UK

Sebastian Johnston, Imperial College, School of Medicine at St. Mary's, National Heart and Lung Institute, UK

Steffan Ahlstedt, Karolinska Institute, Sweden

Christophe von Garnier, Bern University Hospital, Bern Switzerland

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

Louis Rosenthal, National Institutes of Health, USA

Dr Christian Pasquali, OM PHARMA, Switzerland

Dr Deborah Strickland

Prof Sarah Robertson, University of Adelaide. Preventing poor fetal outcomes associated with maternal infection during pregnancy.

Prof Susan Prescott, Perth, Australia. RCT- egg allergy; Preventing poor fetal outcomes associated with maternal infection during pregnancy.

Prof Peter Sly, Queensland. Protection against allergic asthma by immunomodulation.

Prof Richard Saffrey,, Dr David Martino, Melbourne, Australia. Epigenetics in allergic asthma- a twin study.

Prof Mark Kendall, Dr Michael Crichton, Queensland, Australia. Immunotherapy for allergy using nanopatches.

Prof Lou Rosenthal, Virology Division, University Wisconsin, US. Respiratory viral infection and asthma

Dr Phil Stumbles, Murdoch Uni Perth, Australia. Respiratory viral infections

Dr Christophe von Garnier, Bern University Hospital, Switzerland, Nanoparticles; Respiratory viral infections

Dr Fabian Blank, Bern University Hospital, Switzerland, Nanoparticles; Respiratory viral infections

Dr Matt Linden, CMCA UWA, immune development-

Prof Mark Hogarth, Melbourne, Australia. Fc-Gamma Receptors and immune responses in allergic asthma

Dr Anthony Bosco, Perth- viral infection and asthma pathogenesis (animal model)

Dr Debbie Palmer, School Paediatrics and Child Health (SPACH)- allergic diseases/VitaminD

Prof Mark Everard, SPACH, Perth. RSV infection

Dr Christian Pasquali, OM PHARMA, Switzerland, studies on protection against inflammatory mediated disease.

Assoc Prof Alex Larcombe- Clinical Sciences, Lung physiology group, Telethon Kids

Dr Ingrid Laing, Perth- acute asthma exacerbation and viral infection (human

cohort)

Assoc Prof Charlene Kahler, UWA, animal models for bacterial infections

Prof Frode Jahnsen, Oslo, Norway. Dendritic cells in human allergy.

David Proud, University of Calgary, Alberta, Canada

Active collaborations with industry

Dr Deborah Strickland and Prof Patrick Holt, OM PHARMA, Geneva, Switzerland

Active community involvement

Dr Deborah Strickland, secondary school student laboratory projects

Awards

Dr. Elysia Hollams received a Merit Award (Near-miss, \$75,000) from the W.A. Department of Health in recognition of a well-scored NHMRC project grant application in 2013, to enable the application to be made more competitive in the 2015 funding round.

Dr Deborah Strickland

WA Department of Health Fellowship Award

ARC Linkage Infrastructure and Equipment Fund (LIEF): Mass cytometry - a breakthrough in multidimensional systems biology. 2014. Co-chief Investigator, \$440,000;

CHILDHOOD CANCER

Cancers in children comprise many different diseases. More than half of them affect cells of the immune system and the central nervous system, and thus, the most common malignancy in children is leukaemia, followed by brain tumours. In contrast, the most common types of cancer in adults are carcinomas, and they begin in cells that line the surface of the body and internal structures. Despite marked improvements in the cure rates for paediatric cancers, leukaemia 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 US-based Children's Oncology Group (COG). COG is the largest study group of this kind, and 240 hospitals around the globe participate in evaluating better treatments for children with cancer. 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 systems comprise many leukaemia and cancer cell models, and they 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 Heng, J Ford, LC Cheung, AL Samuels and UR Kees, in collaboration with CH Cole, M Crook and AK Charles, 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 confer a growth advantage within the bone marrow. 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. Knocking down CTGF in the same PER-371 cell line we observed corresponding disease outcomes.

Median survival of control PER-371 cells was 67 days, while survival of mice injected with distinct shPER-371 cells was extended to 78 days and 81 days, respectively ($p=0.0002$). These in vivo studies demonstrate that modulation of CTGF expression levels significantly influences survival.

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

Novel CT domain-encoding splice forms of CTGF/CCN2 are expressed in B-lineage acute lymphoblastic leukaemia.

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

Connective tissue growth factor (CTGF/CCN2) has been shown previously to be aberrantly expressed in a high proportion of paediatric precursor B cell acute lymphoblastic leukaemia (pre-B ALL), suggesting a potential oncogenic role in this tumour type. We therefore assessed CTGF mRNA transcript diversity in B-lineage ALL using primary patient specimens and cell lines. CTGF mRNA expression was evaluated by quantitative real-time PCR and Northern blotting. Northern blot analysis of pre-B ALL cell lines revealed non-canonical CTGF transcripts that were expressed in association with the active phase of cellular growth. We performed a structural analysis of CTGF mRNA by nested reverse-transcriptase PCR and observed the



synthesis of several novel CTGF mRNA isoforms in B-lineage ALL cell lines that were uniformly characterised by the retention of the coding sequence for the C-terminal (CT) domain. One of these novel spliceforms was expressed in a majority (70%) of primary pre-B ALL patient specimens positive for canonical CTGF mRNA. These alternative transcripts appear to have coding potential because immunoblots using anti-CTGF antibodies revealed bands of predicted size. This study identifies for the first time alternative splicing of the CTGF gene and shows that a short CTGF splice variant associated with cell proliferation is expressed in most cases of primary CTGF-positive pre-B ALL. This novel variant encoding only the CT domain may play a role in pre-B ALL tumorigenesis and/or progression.

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. Sulphite 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, 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, and single nucleotide variants (SNVs) were called using a GATK pipeline according to best practices guidelines. 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 isoflavone 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, 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: D Anderson, AL Samuels, AH Beesley 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 tumours derived from individual patients. In two of the four leukaemia 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 leukaemia 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.

Pharmacological and molecular analysis of high-risk infant acute lymphoblastic leukaemia.

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

The overall cure rate for children with acute lymphoblastic leukaemia (ALL) has improved significantly with time, and currently exceeds 90%. However, infants less than one year of age at diagnosis remain an exception to this success. Risk factors predictive of an inferior outcome for infants with ALL (iALL) include the presence of a mixed lineage leukaemia (MLL) gene

rearrangement (MLL-r), which occur in up to 80% of cases, hyperleukocytosis at presentation, age less than 90 days at diagnosis and poor response to initial prednisone therapy. Contemporary therapeutic protocols use combinations of drugs, including steroids, alkaloids and anti-metabolites, administered in dose-intensive schedules. However, 5-year event-free survival remains at 16% for infants with MLL-r disease who are diagnosed before they are 3 months old, highlighting the need to identify novel drugs to improve outcome.

Cell lines established from ALL patients with MLL-r disease provide an indispensable resource to examine drug responses. However, in respect to commercially distributed cell lines, there are limited reports that compare their features to those of the matched primary patient specimens, to verify their utility in pre-clinical studies. We previously generated two iALL cell lines with MLL-r and reported their responses to ten currently used chemotherapeutic drugs. These two cell lines demonstrated vastly different responses to drugs such as Cytarabine (ARAC), 6-Mercaptopurine, Dexamethasone, Methylprednisone and L-asparaginase. Identification of novel drug candidates for iALL therapy therefore requires assessment across several patient-derived specimens.

We established additional ALL cell lines from high-risk infants, diagnosed with MLL-r disease before 90 days of age, and performed transcriptome

and genetic analyses of the cell lines and matched primary leukaemia specimens to characterize molecular concordance and divergence. Drug sensitivity was assessed in vitro comprising drugs currently used to treat iALL, FDA-approved cancer drugs and pre-clinical therapeutics targeting features of MLL-r disease, including chromatin, NF- κ B, cyclin dependent kinase 9 and BCL2 function. We report a comprehensive molecular comparison of a panel of iALL cell lines with their corresponding primary material. Our high-throughput drug screens identified several classes of drugs with consistent efficacy, including histone deacetylase inhibitors (HDACi), cyclin dependent kinase inhibitors (CDKi) and proteasome inhibitors (PROTi). Moreover, we found that Romidepsin, an FDA-approved HDACi drug, synergises with ARAC across this panel of patient-derived MLL-r cell lines and also can reduce leukaemia burden in a mouse xenograft model of iALL disease.

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

Dose-dependent effects of histone deacetylase inhibitors on high-risk infant acute lymphoblastic leukaemia cells.

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 less than 40%. MLL encodes a histone methyltransferase (H3K4) that is part of the trithorax complex, an evolutionarily conserved developmental regulator of chromatin structure. Since this aggressive leukaemia is an exemplary tumour driven by epigenomic dysfunction, we have investigated the effects of drugs targeting epigenetic processes, such as histone regulators. Drug actions were examined by flow cytometry to measure cell cycle and chromatin state alterations at single-cell resolution. Cells were harvested, permeabilised and stained with antibodies against H3S10-phosphorylation and either H3K27-acetylation or H3K79-trimethylation. Cell cycle was assessed using propidium iodide staining.

We examined chromatin state following exposure of iALL cells to drugs that function as inhibitors of histone modifying enzymes. Vorinostat, a pan-histone deacetylase (HDAC) inhibitor, was assessed at low and high doses (625 nM and 3 μ M respectively). We also tested effects of an inhibitor of the DOT1L H3K79-histone methyltransferase (3 μ M), and Vincristine (10 mg/ml) - a microtubule inhibitor used as a control cytotoxic compound. Cells were incubated for 24 hours. Cells treated with the low dose of Vorinostat (625 nM) or DOT1L inhibitor were also assayed after 8-days treatment. As expected, Vincristine induced H3S10-phosphorylation indicative of mitosis;

but did not induce changes to histone acetylation or methylation. High dose Vorinostat treatment was associated with accumulation of cells in S-phase and an increased frequency of cells with high levels of H3K27-acetylation and H3K79-trimethylation. Conversely, sub-toxic low dose Vorinostat treatment caused a reduction in global H3K27-acetylation and H3K79-trimethylation, at 24 hours and also after 8-days treatment. The inhibitor of DOT1L histone H3K79-trimethylation caused a dramatic reduction in both H3K27-acetylation and H3K79-trimethylation.

These results reveal contrasting effects of low and high doses of HDAC inhibitors on the chromatin state of iALL cells. Intriguingly, the effects of low dose Vorinostat treatment resembled effects of inhibiting the H3K79-methyltransferase, DOT1L. Further studies are required to define the therapeutic implications of these findings.

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 gene variants involved in DNA repair.

Investigators: AM Gout, RS Kotecha, J Ford, AH Beesley, RW Francis, MN Cruickshank and UR Kees, in collaboration with T Lassmann, Computational Biology.

Acute lymphoblastic leukaemia (ALL) occurring in the first year of life is rare,

accounting for 2-5% of paediatric ALL cases. Infant ALL (iALL) is distinguished by unique clinical and biological characteristics, with an aggressive course. 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 characterised with t(4;11), t(9;11) and t(11;19) the most frequent translocations in iALL. The survival of patients diagnosed before they are 90 days old remains poor at only 16%. 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 investigated ten iALL patients diagnosed with MLL-rearranged ALL, 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). We performed RNA-seq (Illumina, 100bp paired end) on the ten leukaemia specimens, and exome-seq for seven matched remission bone marrow biopsies. 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, including PolyPhen2, Sift, MutationTaster, likelihood ratio test, GERP, PhyloP and CADD, population

allele frequencies (dbSNP, 1000 Genomes and HapMap) and presence in the Catalogue 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 DNA-repair genes harbouring putative damaging SNVs in iALL patient samples compared to controls. Further studies are required to determine the role of these SNVs in infant leukaemogenesis.

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

Analysis of tandem E-box motifs within human complement receptor 2 (CR2/CD21) promoter reveals cell specific roles for RP58.

Investigators: MN Cruickshank, in collaboration with Lawrence J Abraham and Daniela Ulgiati, University of Western Australia.

E-boxes serve as binding sites for E-proteins, including E2A, which play a role in executing B-lineage-specific gene expression programs. However, the mechanisms that restrain E2A activity during lymphoid development are poorly defined. We have previously characterized the basal requirements for transcription of the CR2/CD21



gene and identified tandem E-box elements that are crucial for cell- and B-cell stage-specific expression. Here we investigate tandem E-box motifs, spaced 22 bp apart and within 70 bp of the transcription initiation site, revealing a critical role in controlling CR2/CD21 transcription. These two motifs show opposing function and appear only to be active depending on the cellular context. Furthermore, we have identified E2A transcription factors as binding to one of the E box motifs using EMSA and ChIP analyses; however, as yet unidentified proteins are also binding these functionally important elements. Utilizing a proteomics approach to identify unknown components interacting with E-box site 2 motifs, we successfully isolated and identified RP58 (encoded by RP58/ZNF238/ZBTB18); and reconstituted its binding activity in vitro. Further, in vitro transfection studies confirmed repression specifically through the E-box site 2 repressor element. Conversely, CR2-expression in B cells was associated with E2A and USF binding via E-box sites 1 and 2 respectively and localized chromatin hypersensitivity. Analysis of gene expression compendia in humans and mice reveals co-expression of RP58, E2A and CR2/CD21 in B-cells, supporting a role for these factors in controlling B-cell development or function. Furthermore, RP58 has been defined within a signature gene-expression profile distinctive of a translocation t(1;19)(q23;p13.3) present in paediatric B-cell acute lymphoblastic

leukaemia, raising the possibility that this gene may be involved in normal B-cell development and leukaemogenesis.

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

Focused transcription from the human CR2/CD21 core promoter is regulated by synergistic activity of TATA and initiator elements in mature B cells.

Investigators: MN Cruickshank, in collaboration with Lawrence J Abraham and Daniela Ulgiati, University of Western Australia.

Complement receptor 2 (CR2/CD21) is predominantly expressed on the surface of mature B-cells where it forms part of a coreceptor complex that functions, in part, to modulate B-cell receptor signal strength. CR2/CD21 expression is tightly regulated throughout B-cell development such that CR2/CD21 cannot be detected on pre-B or terminally differentiated plasma cells. CR2/CD21 expression is upregulated at B-cell maturation and can be induced by IL-4 and CD40 signalling pathways. We have previously characterized elements in the proximal promoter and first intron of CR2/CD21 that are involved in regulating basal and tissue-specific expression. We now extend these analyses to the CR2/CD21 core promoter. We show that in mature B-cells, CR2/CD21 transcription proceeds from a focused TSS regulated by a non-consensus TATA box, an

initiator element and a downstream promoter element. Furthermore, occupancy of the general transcriptional machinery in pre-B versus mature B-cell lines correlate with CR2/CD21 expression level and indicate that promoter accessibility must switch from inactive to active during the transitional B-cell window.

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, J Oommen, RW Francis, UR Kees and AH Beesley, in collaboration with AK Charles and CH Cole, 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 Princess Margaret Hospital and at other centres around the world. This now stands a total of 12 such cell lines – to our knowledge, the most comprehensive collection of NMC cell lines in the world. To increase our understanding of the oncogenic mechanism in these NMC cells we have performed next-generation transcriptome and whole-exome sequencing.

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 identified a novel transcript in which Exon 15 of BRD4 was fused to Exon 2 of NUT, therefore differing from all previously published NMC fusion transcripts. Through these studies we now know that there are several other breakpoint positions that feature in this disease and that each of these gives rise to alternative isoforms of the fusion protein. Thus, there are at least six different molecular subtypes of NMC and this is likely to have important implications for patient stratification and clinical outcomes. For example, we have data to indicate that the NMC subtypes may respond differently to currently used chemotherapies. We are now mining the sequencing data from these lines to identify their common

GROUP NAME

(and unique) genetic features and understand the signalling pathways driving 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.

Drug screening in NUT midline carcinoma: the search for a cure.

Investigators: AH Beesley, A Stirnweiss, J Oommen, UR Kees in collaboration with CH Cole, Princess Margaret Hospital, Perth.

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer for which there is no effective therapy; patient survival is less than one year from diagnosis. 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, from those used to treat other solid tumours. 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 a chemical library of > 1200 FDA-approved compounds in NMC vs. non-NMC cell lines.

From this we have identified a shortlist of effective compounds that we are now testing in an expanded panel of NMC cell lines. These represent a number of distinct drug classes including microtubule inhibitors, anthracyclines, topoisomerase inhibitors, antimetabolites, aurora-kinase inhibitors and anti-inflammatory agents, as well as BET inhibitors and the CDK9 inhibitor flavopiridol. Our data show that anthracyclines, topoisomerase inhibitors and microtubule poisons are among the most cytotoxic drug classes for these cells in vitro, but the efficacy of aurora kinase and bromodomain inhibitors varies considerably between NMC cell lines. The CDK9 inhibitor flavopiridol is consistently effective at nanomolar concentrations in vitro and inhibits tumour growth in a subset of NMC mouse xenografts. The microtubule inhibitor vincristine also inhibits tumour growth and increases survival in these mouse models, supporting the continued use of this class of agent to treat patients with NMC. 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.

Laurence Cheung, BPharm (Hons), PhD

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Theses passed

Laurence Cheung, PhD UWA. The role of connective tissue growth factor in hematopoiesis. Supervisors: Professor UR Kees, Professor CH Cole, Dr D Strickland and Dr A Charles.

Rishi S Kotecha, PhD UWA. Rare childhood tumours: Clinical challenges and genetic alterations.

Supervisors: Professor CH Cole, Professor UR Kees and Dr N Gottardo.

Awards

Ursula Kees, Raelene Endersby, Nick Gottardo, Jason Waithman and others. Cancer Council WA / BHP Billiton Infrastructure Grant (2014), \$500,000.

Anja Stirnweiss, Raine Priming Grant (2015-2016): 'Protein signalling networks in NUT Midline Carcinoma (NMC).'

Alex Beesley, Children's Leukaemia and Cancer Research Foundation (CLCRF) Research Fellowship (2013-2015): 'Targeting therapy and disease outcomes in NUT Midline Carcinoma'.

Alex Beesley, CLCRF Project Grant (2014-15): 'Morpholino therapy for childhood cancer'.

Alex Beesley, CLCRF Project Grant (2014-5): 'Finding the most effective therapies for midline carcinoma'.

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

Laurence Cheung, Children's Leukaemia and Cancer Research Foundation Travel Grant.

Ursula Kees, The Kids Cancer Project (2014): Improving the treatment for infants with leukaemia, \$100,000.

Ongoing Awards

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 (2011-2015): Targeting drug-resistance in paediatric acute lymphoblastic leukaemia.

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, Children's Leukaemia and Cancer Research Foundation (CLCRF): Recognition Award (2012-2017): Molecular genetics of childhood cancer.

Ursula Kees, Children's Leukaemia and Cancer Research Foundation (CLCRF) Research Program (2012-2015): Therapy

and molecular genetics of leukaemia in infants.

External Committees

International

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

Ursula Kees, Co-investigator COG-AALL10B1 Study Committee (Children's Oncology Group), Arcadia, CA USA.

Local

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

Invited Presentations

Stirnweiss A, Beesley AH, Kees UR et al (2014). NUT Midline Carcinoma – The search for therapy options to improve the outcome of a fatal disease. EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Barcelona, Spain.

Beesley AH (2014). NUT Midline Carcinoma: What is it, and why should you care? iVEC Supercomputing Annual Symposium, Perth, Western Australia.

Beesley AH (2014). NUT Midline Carcinoma - A pre-clinical assessment of therapy options for a fatal disease. ASMR Scientific Symposium, Perth, Western Australia.

Beesley AH (2014). Researching Childhood Cancer. Rotary-Lions Club South West Bike Trek Fundraiser, Pinjarra, WA.

Kees UR (2014). Pathophysiology of CTGF expression in acute lymphoblastic leukaemia. University Medical Center Utrecht, The Netherlands, October 2014.

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 Antoinette Anazado & Dr Kristy McCarthy, Kids Cancer Centre, Sydney Children's Hospital, Randwick, New

South Wales, Australia.

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 Tumour Research Program

Cancer is a battle too many children and teenagers face every day. It is the leading cause of death by disease among Australian children from birth to age 15. The Brain Tumour research program is a group of dedicated researchers striving to improve cure rates for young people affected by brain tumours. To ensure our research is grounded in clinical practice we have forged strong partnerships between laboratory researchers and paediatric oncologists, pathologists, surgeons, imaging specialists and radiation oncologists. These clinicians share their observations from the clinic with laboratory colleagues and researchers plan their research direction with patients in mind.

Brain tumours are the most common paediatric solid cancer, affecting 200 children in Australia each year. The BTRP, also known as Team BT, is a collaborative group of researchers dedicated to improving our understanding of paediatric brain tumour biology and finding more effective treatments to improve survival

rates and quality of life for patients.

Team BT leaders Nick Gottardo and Raelene Endersby both began their independent research careers at the Telethon Kids Institute following mentored training programs at St Jude Children's Research Hospital (link) in the USA. In recent years, we have established a strong national and international reputation and are recognised as being the largest research team in Australia primarily focussed on paediatric brain tumours. The major goals of our group are intensely focussed on improving the well-being of children with cancer. With strong ties between Princess Margaret Hospital (PMH) (link) and Telethon Kids, leaders Nick & Raelene are acutely aware of what it takes to get a new treatment into the clinic and our research goals are sharply focussed on providing the preclinical evidence required to form the basis of new clinical trials.

The skills of our team members are diverse and include laboratory scientists from academia and industry, clinical oncologists and neuro-surgeons. Each member of the team brings their unique and varied experience to tackle our research questions. Moreover, we collaborate with others who bring valuable expertise. These include, but are not limited to, radiologists (clinical and mouse models), medical physicists (cell and animal imaging), chemists (drug screening), pharmacologists (preclinical testing in mouse models) and bioinformaticists (large scale

analyses of brain tumour genomics).

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).

Characterisation of a Novel Fabp7-CrePR Mouse.

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

Ependymomas are the third most common brain cancer in children. Attempts to determine optimum therapies of ependymoma have been hindered by the low incidence of disease and a poor understanding of the disease's biological characteristics and lack of in vivo and in vitro models. A Fabp7-CrePR mouse is being used to generate a spontaneous mouse model for paediatric ependymoma. This model mimics human disease by alterations in commonly mutated genes



Notch1, Pten, and Cdkn2a. Genetic events are controlled by an inducible Cre/loxP system (CrePR), which is activated by a synthetic steroid RU486. This occurs specifically in radial glia (Fabp7), the candidate stem cell for ependymoma.

This is the first report of temporal and spatial regulation of Cre activity in Fabp7-CrePR mice. Therefore, the characterisation of this inducible system is necessary to determine if CrePR is being activated by RU486 in radial glia. To characterise Fabp7-crePR mice, a reporter Rosa26-LSL-LacZ mouse was bred with Fabp7-crePR knock-in mice to generate offspring where transcription of β -galactosidase does not occur until activation of CrePR using a synthetic steroid RU486. Cre activity was induced at postnatal day 0 (P0) and 7 (P7). Brain tissue from mice was then assessed for Beta-galactosidase using histochemistry and immunofluorescence for Cre mediated recombination.

Beta-Galactosidase staining was observed in cells of the radial glia lineage including astrocytes, Bergman glia and neural progenitor cells. The expression and activity of CrePR in these mice was found to be higher at postnatal day 0 than postnatal day 7, which is consistent with the known patterns of expression of the endogenous Fabp7 gene. Histochemistry assays were possibly underestimating the amount of Cre-mediated recombination when compared to immunofluorescence staining. Therefore further

characterisation is required for this study

This work is supported by the NHMRC, Telethon Adventurers, Australian Postgraduate Award (MA), and Raine Clinician Research Fellowship (NGG).

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.

New and effective combination therapies identified in a mouse model of paediatric medulloblastoma.

Investigators: R Endersby, JP Whitehouse, M Kuchibhotla, T Schoep, H Hii and NG Gottardo.

Background: Medulloblastoma is a metastatic paediatric brain tumour arising in the cerebellum. It is classified into four major subgroups based on clinical and molecular profiles and current standard of care is to treat patients similarly regardless of classification. The clinical interventions of surgery, chemo- and radiotherapy can result in cures but come at a price not obvious by the reported survival statistics due to the collateral damage of healthy tissue by these treatments, which negatively impact patient quality of life.

Objective: Identify new effective therapeutic approaches for medulloblastoma patients.

Results: Using high-throughput, cell-based assays human medulloblastoma cells (n=6) were screened against a library of approximately 3200 compounds, including US FDA-approved drugs. Fifty effective compounds were identified and



further in vitro assessment identified several drugs that enhanced the cytotoxic activity of the clinically-used therapeutic: cyclophosphamide (CPA). A checkpoint kinase inhibitor (CHKi), was further assessed in vivo using mice bearing cortical implants of human medulloblastoma cells. When combined, CPA and CHKi reduced tumour burden as measured by IVIS imaging and significantly increased survival of tumour-bearing animals. Immunohistochemical assessment of tumours the combination treatment significantly decreased the percentage of proliferating (Ki67-positive) cells compared to control or CPA-treated tumours. The combination treatment also significantly induced apoptosis (measured by cleaved caspase 3 positivity) compared with controls.

Conclusion: These data demonstrate our experimental approach has robustly identified effective new therapies for paediatric medulloblastoma, and our findings strongly suggest that the combination of CPA with CHKi may be a promising new treatment for this disease.

This work is supported by the NHMRC, a Telethon-Perth New Children's Hospital Research Grant, the Telethon Adventurers, Raine Clinician Research Fellowship (NGG) and the Telethon Kids Institute.

The PI3-kinase inhibitor BKM-120 enhances the anti-cancer effects of vincristine in in vitro paediatric pineoblastoma models.

Investigators: B Patterson, JP Whitehouse, TD Schoep, NG Gottardo, R Endersby

Pineoblastoma is an invasive paediatric brain tumour of the pineal gland. Only 50% of patients will survive with current treatments which include surgery, radiotherapy and intensive chemotherapy. However, survivors can suffer from long-term detrimental side effects. Our laboratory performed a high-throughput drug screen on paediatric pineoblastoma cell lines to identify potential new treatments, which identified several inhibitors of the phosphatidylinositol 3-kinase (PI3K) pathway as effective. Dysregulation of the PI3K pathway has been identified in many human cancers including the brain tumours medulloblastoma, ependymoma and glioblastoma.

The aim of this study was to evaluate the effect of BKM120 on PI3K pathway activity in, and proliferation of, pineoblastoma cells, and whether BKM120 may enhance the anti-cancer action of current chemotherapeutics.

The effect of BKM120 on PI3K pathway activity in three pineoblastoma cell lines (PER-452S, PER-452A, and PER-453) was determined using immunoblotting. Dose-response assays were performed to determine the sensitivity of these cells to BKM120, or the conventional chemotherapeutics cisplatin, cyclophosphamide, and vincristine using alamar blue assays. Drug-interaction assays were performed to examine the effect of combining BKM120 with these conventional

chemotherapeutics.

BKM120 resulted in a dose-dependent reduction of AKT phosphorylation in pineoblastoma cells indicating pathway inhibition. Furthermore, proliferation was blocked in all three lines at concentrations comparable to conventional drugs. Combination assays with mathematical modelling revealed that BKM120 did not interfere with the anti-cancer effects of cisplatin and cyclophosphamide, but reduced the effect of vincristine when administered simultaneously.

BKM120 effectively inhibited the PI3K pathway and blocked pineoblastoma proliferation. Interaction assays suggested that BKM120 does not enhance the action of current chemotherapeutics when administered simultaneously. This study reveals that drug screening and assessment of novel compounds in pineoblastoma cells can identify therapies with a lack of efficacy, avoiding lengthy and costly in-vivo experiments. Assessment of other compounds identified in the high-throughput screen using a similar pipeline will expedite the discovery of a favorable drug-interaction, which will hopefully lead to improved patient outcomes of pineoblastoma patients.

This work is supported by a Telethon-Perth New Children's Hospital Research Grant, the Cancer Council of WA (BP), Raine Clinician Research Fellowship (NGG) and the Telethon Adventurers.

Testing Novel Treatments for Primitive Neuroectodermal Tumours.

Investigators: Aya Anaout, JP Whitehouse, H Hii, T Schoep, NG Gottardo, and R Endersby.

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, a ubiquitous and evolutionarily conserved signalling cascade influencing numerous cellular functions and frequently deregulated in human cancer. This drug targets the effector AKT. 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) was also recently 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. Bioluminescence was used to monitor xenograft growth and treatment administered once tumours were well established. Outcome was assessed using immunohistochemistry, which revealed increased apoptosis in drug-treated tumours compared to controls.

These studies demonstrate 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 was supported by the Telethon Adventurers.

A novel technique of serial surgical biopsy in a mouse brain tumour model.

Investigators: S Rogers, S Lee, NG Gottardo, and R Endersby

Background: Biopsy is performed clinically to conclusively diagnose a cancer and elucidate the severity of disease. It is often used to tailor treatment to known vulnerabilities in the tumour, such as cancer-specific “targeted” agents. Like human tumours, spontaneous cancers in genetically modified mice carry a range of potentially targetable secondary mutations. Biopsy would greatly enhance the utility of mouse models for preclinical studies using molecularly-targeted therapies.

Objectives: Develop a novel method of serial biopsy in mice, assess morbidity associated with the technique and determine the quality and utility of tissue samples obtained.

Results: To determine the feasibility of brain biopsy, we utilised an intracranial implant model of glioblastoma, driven by activation of EGFR. We previously showed that EGFR can be inhibited in brain tumours using the pan-ERBB inhibitor dacomitinib and that inhibition prolongs animal survival. We developed a micro-dissection technique that retained structural and molecular features of the brain tumour. We were able to successfully detect active EGFR in the biopsy sample and measure the intratumoural response following systemic administration of dacomitinib. Neurological impairment of animals following the procedure was minimal and reversible.

Conclusions: Serial brain biopsies in

mouse models are possible with little impairment. Tissue samples can be obtained reliably and retain enough histological features for reliable assessment of tumour histology and molecular pathology. Analysis of tumour samples could identify the presence of drug-targetable alterations in murine cancers and serial biopsy can monitor the magnitude and duration of response to treatment in a single animal.

This work is supported by the Ethan Davies Scholarship for Brain Cancer Research, the Telethon Adventurers and Raine Medical Research Foundation (NGG).

Combination of novel drugs with conventional chemotherapies for the treatment of medulloblastoma.

Investigators: K Smith, T Schoep, P Dallas, R Endersby, NG Gottardo.

Medulloblastoma is a malignant embryonal brain tumour, and is the most significant cause of paediatric cancer mortality. A plateau in survival rates for children with medulloblastoma has been reached and novel therapies are urgently needed to improve cure rates and minimize the treatment related side effects. Gene expression profiling of human medulloblastoma primary samples revealed the over-expression of a gene known as cellular FAS-like IL-1 β -converting enzyme-inhibitory protein (cFLIP) that normally functions to prevent apoptosis by inhibiting the activation of caspase 8. This protein is also over-expressed in other cancers and is thought to be involved in

resistance to anti-cancer therapies. cFLIP has been shown to be down regulated by the compound CDDO, and its derivatives CDDO-Imidazolamide and CDDO-methyl. This study proposes that the CDDO-based compounds inhibit proliferation of medulloblastoma cell lines, and that these drugs are additive with conventional chemotherapies.

To assess the effect of CDDO on three human medulloblastoma cell lines the assay conditions for cellular proliferation were optimized. We confirmed that three medulloblastoma cell lines produced cFLIP and were sensitive to CDDO based compounds at effective doses between 0.27 and 1.05 μ M. It was also observed that at concentrations below 0.22 μ M these drugs stimulated cellular growth. The combined effect of each CDDO based compound with the conventional chemotherapies used to treat medulloblastoma, cisplatin, vincristine, cyclophosphamide, was assessed in cell line based drug interaction assays. Using three different algorithms for the analysis of drug interaction: the Chou-Talalay, BLISS independence and, Loewe additivity method, it was shown that all combinations of the CDDO-based molecules and the standard chemotherapeutics were antagonistic.

As a result, results from this study suggest that the CDDO and the derivatives CDDO-Imidazolamide and CDDO-Methyl, are not suitable for preclinical evaluation in animal models of medulloblastoma in combination with either of the standard chemotherapies.



This work is supported by the NHMRC, Princess Margaret Hospital Foundation Translational Research Grant, Raine Clinician Research Fellowship (NGG), and the Telethon Adventurers.

Oncogenic transformation of human neural stem cells.

Investigators: JP Whitehouse, R Endersby, C George, 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 Whitehouse 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, and the Telethon Adventurers

Molecular genetics of novel paediatric brain tumour models.

Investigator: R Endersby, M Kuchibhotla, H Hii, S Lee, N Gottardo

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.

Investigating the role of DACH1 and miR-200b in Group 4 medulloblastoma pathogenesis.

Investigators: C George, J Bearfoot, and PB Dallas.

Medulloblastoma is the most common malignant childhood brain tumour, and the most significant cause of childhood cancer-related mortality. Four core molecular sub-groups exist, with distinct features and responses to treatment. The current clinical management of patients does not account for this molecular variation, and many patients may receive sub-optimal treatment. To address this, targeted therapies for each molecular sub-group would be ideal. Unfortunately, for the more aggressive Group 3 and Group 4 sub-groups, the underlying mechanisms of pathogenesis remain poorly understood. The current challenge is to identify the key tumour suppressors or oncogenes involved in Group 3 and Group 4 pathogenesis, which may ultimately lead to the development of new therapeutic targets. Transcriptional profiling studies of medulloblastoma have identified numerous genes commonly affected in other cancers, which may also contribute to medulloblastoma pathogenesis.

One potential candidate is Dachshund Homolog 1 (DACH1), which has up-regulated expression across all medulloblastoma sub-groups, relative



to normal cerebellum. Oncogenic over-expression of DACH1 has been demonstrated in both ovarian and colorectal cancers, and is associated with cancer progression and invasiveness, but has not previously been linked to medulloblastoma pathogenesis. MicroRNAs (miRNAs) have been implicated in the initiation and progression of many cancers and may mediate the abnormal expression of DACH1 in medulloblastoma. Analysis of the DACH1 3'UTR using TargetScan revealed potential binding sites for nine individual/clusters of miRNAs. One putative miRNA is miR-200b, belonging to the highly conserved microRNA-200 family (miR-200). We identified an association between high levels of DACH1 expression and low level of miR-200b and further assessed the regulation of DACH1 by this miRNA in medulloblastoma cell lines.

This work was supported by the Telethon Adventurers (PD) and Cancer Council of Western Australia (CG).

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 Smoothed (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

Co-heads

Raelene Endersby, PhD

Nick Gottardo, MB ChB FRACP PhD

Research Staff

Peter Dallas, PhD

Tobias Schoep, PhD

Jacqueline Whitehouse, PhD

Hilary Hii, BSc Hons

Mani Kuchibhotla, BSc MSc

Postgraduate Students

Mathew Ancliffe, BSc, PhD candidate

Sasha Rogers, BSc(Hons) MBBS
MRCS(ed), MPhil student

Aya Arnaout, BSc, Honours student

Kathlyn Smith, BSc, Honours student

Brett Patterson, BSc, Honours student

Courtney George, BSc, Honours
student

Other Students

Brooke Strowger, Murdoch University

Theses passed

Rishi S Kotecha, PhD UWA. Rare childhood tumours: Clinical challenges and genetic alterations.

Supervisors: Professor CH Cole, Professor UR Kees and Dr N Gottardo.

Aya Arnaout (BSc), Honours thesis, Murdoch University. Testing Novel Treatments for Primitive

Neuroectodermal Tumours.

Supervisor: Dr Raelene Endersby

Brett Patterson (BSc), Honours thesis, University of WA. The PI3K inhibitor, NVP-BKM120, does not interact synergistically with cisplatin, 4-HPC or vincristine in in vitro paediatric pineoblastoma models.

Supervisors: Dr Raelene Endersby, Dr Jacqueline Whitehouse, Dr Fiona Pixley

Courtney George (BSc), Honours thesis, Edith Cowan University. Investigating the role of DACH1 and miR-200b in Group 4 medulloblastoma pathogenesis.

Supervisors: Dr Peter Dallas, Dr Mel Ziman

Kathlyn Smith, (BSc), Honours thesis, Murdoch University. Targeting Apoptotic Pathways in Medulloblastoma.

Supervisors: Dr Tobias Schoep, Dr Peter Dallas, Dr Garth Maker

Awards

Ursula Kees, Raelene Endersby, Nick Gottardo, Jason Waithman and others. Cancer Council WA / BHP Billiton Infrastructure Grant (2014), \$500,000.

Nicholas Gottardo, Raelene Endersby, Anang Shelat, Telethon-Perth Children's Hospital Research Fund (2014-2016), \$198,344.

GROUP NAME

Ongoing Awards

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

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

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

External Committees

International

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.

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: Effective science communication for EMCRs. April 2015. Adelaide, Australia.

Raelene Endersby, national conference organising committee, EMBL Australia PhD Program. June 2015. Perth, Australia.

Local

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

Raelene Endersby (June 2014) High-throughput drug screening for childhood brain tumours: translating hits into the clinic. The Children's Hospital at Westmead, Kids Research Institute. Sydney, Australia.

Raelene Endersby (July 2014) High-throughput drug screening for childhood brain tumours: translating hits into the clinic. Peter MacCallum Cancer Centre. Melbourne, Australia.

Raelene Endersby (November 2014) Understanding childhood brain cancer and finding new ways to improve patient outcomes. Curtin University. Bentley, Australia.

Nick Gottardo (January 2014) Update

on the upcoming Children's Oncology Group's (COG) frontline average risk medulloblastoma clinical trial Medulloblastoma In the Mountains, St Moritz, Switzerland.

Nick Gottardo (May 2014) Clinical trials in the Children's Oncology Group - the past and the future Perth Cancer Club, Perth, Australia.

Nick Gottardo (June 2014) Summary talk for PNET and Rare Tumours Session. International Symposium Paediatric Neuro-Oncology (ISPNO), Singapore.

Nick Gottardo (June 2014) Paediatric Oncology, from Bench to Bed. Cure Brain Cancer Foundation International Scientific Meeting, Sydney, Australia.

Nick Gottardo (October 2014) Princess Margaret Hospital and Telethon Kids Institute Annual Research Symposium, Perth.

Research Hospital, USA.

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

Dr Charles Eberhart, Johns Hopkins Medicine, USA.

Dr Anang Shelat, St Jude Children's Research Hospital, USA.

Dr Christa Nath, Children's Hospital at Westmead, NSW, Australia.

ACTIVE collaborations

Brain Cancer Discovery Collaborative (BCDC). 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), Associate Prof Stephen Rose (CSIRO, QLD), Associate Prof Geraldine O'Neill (Children's Hospital at Westmead, NSW).

International Medulloblastoma Working Group (50 members).

Prof Amar Gajjar, St Jude Children's

CYSTIC FIBROSIS

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. Since 2012, Professor Stick and A/Prof Sarath Ranganathan (VIC) were supported by a US Cystic Fibrosis Foundation Therapeutics grant 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 initiated since 2012 include investigations into mucus, hypoxia and the respiratory microbiome in progressive CF lung disease with the University of North Carolina, USA and the role of bioactive lipids in resolution of inflammation and tissue remodelling with Erasmus Medical Centre, Netherlands. Many factors contribute to exaggerated inflammatory responses observed in the CF lung; we have observed dysfunctional immune responses to common viruses and using systems biology approaches, we are identifying responses to viruses and bacteria that are pro-inflammatory and modifiable with existing and novel agents. Our data confirm that these are present soon after diagnosis, associated with disease progression and present a range of therapeutic targets.

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. In 2013, in a landmark paper, we published the first data demonstrating that a biomarker measured at 3 months can predict structural lung disease outcomes at 1 and 4 years of age. We have also developed the first outcome measure (a quantitative CT method) to accurately reflect early structural disease in CF that can pave the way to regulatory studies of new therapies in young children with CF. 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 since 2012 to investigate different aspects of lung structure/function and disease progression.

Funded by: NHMRC, NIH, UWA, Lung Institute of WA, US Cystic Fibrosis Foundation Therapeutics

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.

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 at Princess Margaret Hospital. Our psychosocial data have begun to identify significant impacts on children with CF and their families. These data provide important, unique opportunities to assess child and family psychosocial distress, quality of life, anxiety on academic achievement and other outcome measures and to develop effective interventions.

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)

Professor Graham Hall (Paediatric Respiratory Physiology)

Dr André Schultz, (CF Centre Director, Princess Margaret Hospital)

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 Andrew Chong – Program Manager

Mr Marc Padros-Goossens - Data
Manager

Dr Lidija Turkovic – Biostatistician

Dr Kathryn Ramsey - Research Officer,
Paediatric Respiratory Medicine

Dr Shannon Simpson - Research Officer,
Paediatric Respiratory Medicine

Dr Erika Sutanto - Research Officer

Ms Kak Ming Ling – Research Assistant

Mr Luke Berry – Research Assistant

Dr Elizabeth Starcevich – Research
Officer/study coordinator

Ms Georgia Banton – Research
Assistant, Paediatric Respiratory
Medicine

Ms Anneli Robbshaw – Clinical Trials
Coordinator

Ms Lucy McCahon – Clinical Trials
Coordinator

Ms Annemarie Naylor – Project Officer

Ms Nicole Shaw - Research Assistant

Ms Kelly Martinovich - Research
Assistant

Ms Pari Tackle - Research Assistant

POSTGRADUATE STUDENTS

Mr Tim Rosenow – PhD candidate

Mr Luke Garratt – PhD candidate

Ms Cindy Branch-Smith – PhD
candidate

Mr Thomas Iosifidis - PhD candidate

Mr Kevin Looi - PhD candidate

THESES PASSED

Lauren Mott – PhD

AWARDS

Kathryn Ramsey

North American Cystic Fibrosis
Conference Young Investigator Award

Dr Louisa Alessandri Memorial Fund
Prize for Scientific Publication

2014 AJRCCM publication editorialised

Luke Garratt

TSANZ Ann Woolcock Young
Investigator Award

Poster Prize - Child and Adolescent
Health Research Symposium

Tim Rosenow

TSANZ CF SIG Prize

Vertex Cystic Fibrosis Research Award

Lauren Mott

UWA Most Cited Articles

EXTERNAL COMMITTEES

International

Steve Stick

Scientific Board - Sophia Foundation,
Rotterdam

Graham Hall

ERS College of Experts

National

Steve Stick

Grant Review Panel – NHMRC

Local

Nick de Klerk

Clinical Drug Trial Committee, Sir Charles Gairdner Hospital

Western Australian Mesothelioma Register Committee

Busselton Population Medical Research Institute Inc, Board

Busselton Population Medical Research Institute Inc, Research Committee

Director, Western Australian Twin Register

Expert Reference Group, Australian Twin Registry

Western Australian Medical Radiation and Cancer Working Party

Data Safety Monitoring Committee - RCT Intragastric Balloon in Obese Adolescents

Patron, Perth and Districts Multiple Birth Association

INVITED PRESENTATIONS

Steve Stick

Plenary Early Cystic Fibrosis Lung Disease. Irish Thoracic Society Dublin,

Ireland.

Symposium Early CF Lung Disease. TSANZ Adelaide.

Symposium Imaging and Structural Lung Disease. North American CF Conference Atlanta, USA.

Graham Hall

Laying the foundations in childhood for healthy or disease adult lungs. Joint New Zealand TSANZ and ANZSRS annual meeting.

Tim Rosenow / Conor Murray

What's around the corner in chest CT. CHESTRAD Melbourne 2014.

Cindy Branch-Smith

Arresting' psychological issues for better health outcomes in parents of infants and young children with cystic fibrosis. European Cystic Fibrosis Conference Psychosocial Special Interest Group.

ACTIVE research 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 Richard 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

Bob Scholte - Erasmus MC, Rotterdam

Professor Marcus Mall - University of Heidelberg

ACTIVE collaborations with industry

Ataluren – USA

Boehringer-Ingelheim

Parion – USA

Vertex – USA

ACTIVE involvement with the community

Type of involvement, organisation, state or country

Cystic Fibrosis WA – CF community engagement and research update,

funding

Cystic Fibrosis Australia - CF community engagement, funding

Translation

The COMBAT CF clinical trial, the first interventional trial for prevention of lung disease in infants, is ongoing. This is a multi-centre study to test the efficacy of azithromycin for the primary prevention of bronchiectasis in children with CF. Recruitment on the study is ongoing, with more than half of the target 130 subjects recruited from sites in Australia and New Zealand. Our goal is to eventually ensure that a clinical trial is available to every child born with CF.

DIABETES AND OBESITY

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 2014, 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. The group has also recently been recognised for its work with the award of the jointly funded NHMRC/JDRF Centre of Research Excellence.

Type 1 Diabetes

Clinical Prof TW Jones

Associate Clinical Prof EA Davis

EPIDEMIOLOGY

Epidemiology of childhood diabetes in Western Australia

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

Funding Source: Department of Endocrinology & Diabetes, PMH

The objectives of this study are:

- To study the epidemiology of childhood diabetes in Western Australia from 1985 onwards
- To look 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 modifiable risk factors that may be contributing to the increasing number of children being diagnosed with diabetes
- To characterise the clinical course of diabetes in this population-based cohort of childhood diabetes and

the development of complications of diabetes

- To analyse the effects of changes in treatment regimens and clinical management strategies on the rates of complications of diabetes
- To periodically evaluate the completeness of ascertainment of the Western Australian Children's Diabetes Database

These aims will be achieved by analysis of data from the Western Australian Children's Diabetes Database, together with data linkage to other core data resources in the Western Australian Data Linkage Unit. The study population will be all children diagnosed with childhood diabetes under the age of 15 years, who were resident in Western Australia at the time of diagnosis. The study period is from January 1985 to the most recent years available. There are over 1500 cases in the diabetes register at Princess Margaret Hospital that meet these inclusion criteria.

Epidemiology of hypoglycaemia in childhood-onset diabetes in Western Australia

Investigators: Tim Jones, Liz Davis, Matt Cooper

Funding Source: Internal Funds

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 on 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.

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

Funding Source: Diabetes Research Fund

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.

TrialNet: Pathway to Prevention

Local Investigators: Tim Jones, Liz Davis

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

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)

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:

1. 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.
2. To examine the accuracy of TrialNet measures in predicting future T1D.
3. To characterize the progression of immunologic abnormalities in the development of T1D by serially studying islet autoantibodies and immune mechanistic studies.
4. 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.

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, Alexandra Tully

Funding Source: NHMRC 1025082

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.

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

Funding Source: Pfizer APEC Research Grant

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 \leq 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.

Low glucose suspend study

Investigators: Tim Jones

Study Staff: Jennifer Nicholas, Adam Retterath

Funding Source: Juvenile Diabetes Research Foundation

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 6 months 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).

Effect of blood glucose levels on the amount of glucose needed to maintain stable blood glucose levels during and after moderate intensity exercise in young people with type 1 diabetes.

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

Study Staff: Nirubasini Paramalingam,

Adam Retterath, Heather Roby; Ray Davey;

Funding Source: Internal

Current recommendations for carbohydrate supplementation to prevent exercise-induced hypoglycaemia in individuals with type 1 diabetes (T1D) do not take into account blood glucose levels during exercise. Our objective was to investigate the effect of blood glucose levels on carbohydrate requirements to maintain stable glycaemia during exercise in individuals with T1D at basal insulin levels and to determine the underlying glucoregulatory mechanisms.

We subjected eight healthy individuals with T1D to a euglycaemic clamp, whereby euglycaemia was maintained by infusing insulin at basal rates with concomitant infusion of deuterated glucose for determining glucose kinetics. Participants were then randomized to undergo either euglycaemic or hyperglycaemic clamp, following which they performed 40 minutes of exercise at 50% VO₂peak, on 2 separate days using a randomised counterbalanced study design. The glucose levels maintained during euglycaemic and hyperglycaemic clamp was 4.5-6.0 and 9.5-10.5mmol/L respectively. The glucose infusion rate (GIR), levels of glucoregulatory hormones and rates of glucose appearance (Ra) and disappearance (Rd) were compared between conditions.

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

Funding Source: Pfizer APEC Research Grant; PMH Foundation Grant

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.

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

Funding Source: NHMRC

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.

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

Funding Source: NHMRC

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.

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 Roby

Funding Source: NHMRC

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.

TECHNOLOGICAL ADVANCES

Predictive low glucose suspend study – Stage2

Local Investigators: Liz Davis; Tim Jones; Mary Abraham

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

Funding Source: JDRF

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.

Closed Loop Study – Treat To Range

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

Study Staff: Julie Dart; Adam Retterath; Jennifer Nicholas

Funding Source: NHMRC

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).

Part 1 and part 2 are complete and have presented at international meetings in 2014.

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;

Funding Source: NHMRC

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.

Overnight glucose control with hybrid closed loop system in patients with type 1 diabetes

Local Investigators: Martin de Bock; Tim Jones; Liz Davis; (Colaboration with St Vincents hospital in Melbourne)

Study Staff: Julie Dart; Carolyn Berthold;

Funding Source: NHMRC

The aim of this study is to see if the Medtronic hybrid closed loop system, a portable artificial pancreas can be safely used in the home. The system consists of a glucose sensor that sits under the skin, an insulin pump that delivers insulin and an Android-based smartphone that contain the maths program to calculate the insulin needed. Patients will use the closed loop system at home, after they have spent one night in the hospital getting used to the equipment. Apart from blood glucose levels, we will see how it benefits sleep quality, cognition, and quality of life.

Feasibility of 24-hour hybrid closed loop insulin delivery in free living conditions

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

Study Staff Julie Dart Carolyn Berthold

Funding source JDRF

The aim of this study is to see if the Medtronic hybrid closed loop system, a portable artificial pancreas is feasibly to use in the home. The system consists of a glucose sensor that sits under the skin, an insulin pump

that delivers insulin and an Android-based smartphone that contain the maths program to calculate the insulin needed. Patients will learn to use the device for 2 days in hospital, and then for 5 days at home. Their results will be compared to when they use their insulin pump as normally. This study is now complete and has been presented at an international conference

COMPLICATIONS

Adolescent type 1 diabetes cardiovascular 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

Funding Source: JDRF; BHF

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.

Aussi-AdDIT

Local Investigators: Tim Jones; Liz Davis

Study Staff: Julie Dart; Alison Roberts; Adam Retterath

Funding Source: NHMRC Grant #632521

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, a1MT and heart rate variability measures, after 4 years duration from baseline.

Neurocognitive outcomes of children with type 1 diabetes mellitus

Investigators: Tim Jones; Mike Anderson; Liz Davis

Study Staff: Kaitie McNamara; Nooshi Rath

Funding Source: PMH Foundation; APEG grant

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 T1DM'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.

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;

Funding Source: NHMRC; JDRF

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.

Oral Insulin Trial

Local Investigators: Tim Jones; Liz Davis

Study Staff: Julie Dart; Heather Roby; Adam Retterath

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

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.

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

Funding Source: Departmental

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

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

Funding Source: Pfizer APEC grant # WS1836718

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.

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 Intra gastric Balloon

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

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

Funding Source: NHMRC # 634308; Pfizer APEC Grant

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 be recruited to the study.

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

Funding Source: Unfunded

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

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

Funding Source: Departmental

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 register has consistently been over 99%. This complete, population-based data source is invaluable for studying the epidemiology of childhood onset diabetes in Western Australia.

Australian Childhood Diabetes DNA Repository

Investigators: Grant Morahan; Tim Jones; Liz Davis

Study Staff: Heather Roby

Funding Source: NHMR Enabling Grant

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.

Longitudinal Type 1 and 2 Diabetes Plasma and Serum Repository

Investigators: Tim Jones; Liz Davis

Study Staff: Adam Retterath

Funding Source: Internal Funds

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.

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

Funding Source: Departmental

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.

A Database of the Complications of Obesity in Children

Investigators: Liz Davis; Jacqueline Curran

Study Staff: Rachele Kalic

Funding Source: Departmental

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: Rachele Kalic; Adam Retterath

Funding Source: NHMRC Enabling Grant & Internal Funds

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.

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 Notre 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 (TKI)

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

Tully, Alexandra BN, Post-Grad Dip (Midwifery)

Berthold, Carolyn BSc (Nursing)

Cole, Carol BN, CDE

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

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

Good, Leticia BPsych, MSocRes (Social research methods)

Roby, Heather BSc

Czank, Charles BSc (Hons), PhD

Makin, Janet BBus (info processing)

Research Staff (PMH)

Dr Abraham, Mary

Dr Curran; Jacqueline

Dart, Julie; CRN

Dr de Bock, Martin

Roberts, Alison; CRN; MSc candidate

Dr Shetty, Vinutha

Dr Siafarikas, Aris

Dr Chetty, Tarini

Dr Rath, Nooshi

Dr Kiranjit Joshi

Clapin, Helen BSc. Grad Dip Comp;

MPH

Postgraduate Students

Cooper, Matthew- PhD candidate

Curran, Jacqueline- PhD candidate

Kalic, Rachelle – M App Econ Candidate

Nicholas, Jennifer- MSc Candidate

Shetty, Vinutha- PhD candidate

Soon, Wayne BSc (Hons); PHD candidate

Hamidi, Ana MBB; PhD candidate

Research Support

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

Awards

Dr Vinutha Shetty – RACP Trainee Research Award, 2013

APEG New investigator award 2014

Pfizer Reasearch APEC Grant 2015

Dr Mary Abraham – RACP Advance Trainee; WA, 2013

Telethon Fellowship, 2013

Dr Aveni Haynes - 2014 Australasian Paediatric Endocrinology Group

Travel bursary

Dr Mary Abraham –Telethon Fellowship, 2013

Trainee Research Award of the WA state branch of RACP 2013

Trainee Research Award of the WA state branch of RACP 2014

External Committees

International

Tim Jones. International Journal of Diabetes and Clinical Research- Editorial Board - 2015

Tim Jones. JDRF PEAK Expert Panel - Member 2014 – Ongoing

Tim Jones. International Hypoglycemic Study Group – Member 2013-ongoing

Tim Jones. JDRF Artificial Pancreas Consortium – Member 2011-ongoing

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

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

INTERNATIONAL

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. CME Symposium: Waiting for Closed Loop – tapping the full potential of advanced diabetes technology in today's clinical practice. American Diabetes Association, 72 Scientific Sessions, Philadelphia PA, USA June 2012.

Tim Jones. Technology in Diabetes Therapy. Australasian Paediatric Endocrine Group: Annual Scientific Meeting, New Zealand, July 2012.

Tim Jones. The use of an automated glucose control system for overnight



glucose control in adolescents with Type 1 Diabetes. The Annual Rachmiel Levine Diabetes & Obesity Symposium. Pasadena, California, USA March, 2013.

Tim Jones. China National Pediatric Endocrine Conference. Xia men, China, October 2013

Tim Jones. Hypoglycemia in Diabetes: risks, management and prevention. 34th Annual Meeting of the Australasian Neuroscience Society. Adelaide, Australia, January, 2014.

Tim Jones. Managing Exercise in Type 1 Diabetes. Joslin Seminar 2014. Boston, February, 2014.

Tim Jones. Technology to Prevent Hypoglycemia. 2014 American Diabetes Association Scientific Sessions. San Francisco, California, June, 2014.

Tim Jones. Exercise and Hypoglycemia. 2014 American Diabetes Association Scientific Sessions. San Francisco, California, June, 2014

Tim Jones. Exercise in Children with Diabetes. 2014 American Diabetes Association Scientific Sessions. San Francisco, California, June, 2014

Tim Jones. Hypoglycemia Prevention in Children with Type 1 Diabetes. ISPAD. Toronto, September, 2014

Tim Jones. Hypoglycemia and Glycemic Targets. Panel Discussion and Presentation. EASD Annual meeting. Vienna, Austria 2014

NATIONAL

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.

Tim Jones. Exercise and Hypoglycemia in diabetes. Annual Scientific Meeting 2014 of the Australian Diabetes Society. Melbourne. Australia. August 2014.

Tim Jones. Hypos - sugar, suspend or sprint? 8th Annual Australian Paediatric Society Meeting. Canberra. Australia. October 2014.

Tim Jones. World Diabetes Day NSW. Australia. November 2014

Tim Jones. AstraZeneca Post Graduate Weekend. March 2015

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 Paediatric 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 Carmel Smart: John Hunters Hospital for Children, NSW

Prof Ranjaney Thomas: Diamantina Institute, Qld

Prof Donna Cross: Telethon Kids Institute

Associate Prof Liz Geelhoed: University of Western Australia

Professor Bill Tamborlane: Yale University

Professor Margaret Grey: Yale University

Professor Stuart Weinzmer: Yale University

GENETICS AND HEALTH

Our research focuses on using genomics and transcriptomics to understand complex diseases, helping us to find better drugs and vaccines. Highlights of our research for 2014 include:

Visceral leishmaniasis is a parasitic disease found in resource poor tropical countries and is life-threatening in susceptible individuals. Drugs are toxic, and no vaccines are available. We employed genomics to identify the major genetic risk factor for visceral leishmaniasis in India and Brazil, and have now used biochemical techniques to identify parasite antigens that bind to the molecules encoded by this major histocompatibility complex gene for presentation to the immune system. We also used a genome-wide approach on Raine Study data to show that the same gene determines response to the pneumococcal surface protein C of gram positive *Streptococcus pneumoniae* pneumococci, invasive forms of which are capable of causing life-threatening pneumococcal sepsis and meningitis. Both studies are helping us to design vaccines that will specifically aid in protecting susceptible individuals.

Toxoplasma parasites are common globally, with 30-40% of Australians infected. The parasite causes serious problems if mothers become infected for the first time during pregnancy and pass the parasite across the placenta to the developing baby. Using transcriptomics we have demonstrated that *Toxoplasma* causes changes in

expression of host genes in a pathway influencing mitochondrial dysfunction that could relate directly to congenital clinical signs being focused in the eye and brain. This provides support for repurposing of drugs currently used to treat genetic eye and brain diseases that are associated with mitochondrial dysfunction.

INFLAMMATION

Members of the Inflammation group are studying both the positive and negative effects of UV exposure. Dr Jason Waithman's group is studying melanoma development (UV exposure is the strongest risk factor for melanoma development) and potential immunotherapeutic approaches to destroy it. Drs Prue Hart and Shelley Gorman are leading teams to study the positive effects of UV exposure on reducing several significant health issues, namely autoimmune diseases and obesity, respectively.

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 melanoma and non-melanoma 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 and 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. Further in 2013 and 2014, we demonstrated that exposure of the shaved skin of mice to UV radiation could also reduce weight gain of mice on a high fat diet and that this effect was not due to UV-induced vitamin D. All our studies are important as they tell us that a balance of sun exposure is required. We hear a lot about avoiding sun

but more data are accumulating that there are a large range of benefits for health from sensible safe exposure to moderate sun. With further research, we believe that the right balance of sun exposure will be determined for public health advice. We believe that we are studying issues important to the health of children and we would like to develop, in time, guidelines tailored for sun exposure of children.

In 2014 with the award of a large NHMRC grant, we began translational studies of the effect of UVB exposure on the development of autoimmunity in humans. The trial involves participants with an early form of multiple sclerosis. They have had a first demyelinating event but are not classified as clinically definite multiple sclerosis until they have had a second event. We propose that phototherapy with UVB light can dampen or reverse their disease course. Using preclinical models, in 2014 we began studies of the effect of UVB on reducing the pathology of another immune-mediated disease, namely Crohn's Disease.

The effects of sun exposure can be long-lived for several weeks. With immune cells regularly turned over, we believe that signals must be sent from UV-irradiated skin to the bone marrow which is the powerhouse for immune cell development. In 2014, studies continued to focus on the effects of UV irradiation of skin on blood precursor cells in the bone marrow. Erythematous 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. We have 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 E2. 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 D3 in control of immune cell activity and asthma and obesity models in mice. Humans obtain 90% of their vitamin D3 from UV irradiation of skin so it has been proposed by us, and others, that UV-induced Vitamin D3 may contribute to the immunomodulatory effects of UV. We have examined the effect of vitamin D3 in excess (painted onto

the skin of mice with normal levels of vitamin D3) and in deficiency (mice were fed diets restricted in vitamin D3). We discovered that male vitamin D3-deficient mice were unable to respond to UVB irradiation of skin for vitamin D3 production. Thus, if the male mice responded to UVB for regulation of immunity, this was not via the modulatory properties of vitamin D3. This finding has given us an exciting and ongoing approach to analyse the relative contribution of vitamin D3 and other UV-induced mediators to the immunomodulatory properties of UV irradiation. This finding will help us determine the relative role of UV and vitamin D3 in regulating Crohn's Disease. Furthermore, we have shown that vitamin D3 and UV irradiation of skin have different effects on reducing the symptoms associated with obesity.

During 2014, 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 Career Development Fellow, is focusing on harnessing the power of the immune system to eradicate primary and metastatic melanoma. T cells play a pivotal role in the control and clearance of tumours such as melanoma. Dendritic cells control these T cell responses and he is interested in the type of



instructions specific dendritic cells are providing to T cells during melanoma. His team has recently identified the dendritic cells that are involved in coordinating T cell immunity to cutaneous melanoma. They are actively developing a vaccine that specifically targets these dendritic cells in order to stimulate and activate T cells to expand and attack established tumours.

Another focus of the lab is to improve existing immunotherapies that have enormous potential to transform how oncologists treat patients with cancer. Adoptive T cell therapy was recently selected by the journal *Science* as one of the most important breakthroughs in cancer immunotherapy. However, this treatment doesn't help everyone and further refinements will improve patient outcome. His team is investigating whether type I interferon can enhance the therapeutic efficacy of adoptive T cell therapy.

UVB phototherapy for participants with an early form of multiple sclerosis

Sian Geldenhuys, Prue Hart, Robyn Lucas, Allan Kermode, Bill Carroll, David Nolan, David Booth, Judy Cole

Latitude gradients for the incidence of multiple sclerosis are well established, with more disease at higher latitudes when there is reduced sun. Exposure to sun has been linked with the initiation and progression of MS, and there is evidence that sun exposure is important at all stages of life for MS pathogenesis, even in utero. Many

believe that a lack of UV-induced vitamin D is responsible, but vitamin D supplementation trials have not shown the reduced disease progression that was hoped for. We propose that UV via vitamin D-independent pathways may be responsible. We have initiated a trial of narrow band UVB phototherapy for participants diagnosed with their first demyelinating event in the last 120 days. Participants are randomised to receive, or not receive, UVB phototherapy (24 sessions over 8 weeks). Blood is taken for phenotyping of immune cell subsets in their blood, and biobanking, over a 12 month period. We believe that this is the first trial in the world of UVB phototherapy for participants with Clinically Isolated Syndrome. The trial is called PhoCIS as it is Phototherapy for participants with Clinically Isolated Syndrome.

Funded by NHMRC

The effect of vitamin D and UV radiation on a preclinical model of Crohn's disease

Simon Ghaly, Prue Hart

Low vitamin D levels have been associated with increased incidence of Crohn's disease. However supplementation trials have not generally been successful. It is possible that low vitamin D levels merely reflect low sun exposure and that exposure to UV may be a more realistic treatment strategy. A preclinical model of Crohn's Disease was established using dextran sulphate delivered in drinking water. Mice were fed deficient, sufficient and

excessive levels of vitamin D in their diets, and this was superimposed with UV phototherapy (low dose twice weekly). The preliminary results show that UVB irradiation was protective for the pathology of Crohn's Disease in mice on a vitamin D-deficient diet. However the mice on the diet containing the highest levels of vitamin D had the worst pathology. Assessment of all the tissues removed from the mice is ongoing.

Funded by special grant to Simon Ghaly by Gastroenterology Society of Australia

Effect of UV irradiation of skin on the glycolytic activity of dendritic cells generated by culture from the bone marrow. Is an epigenetic event involved?

Terry McGonigle, Royce Ng, Prue Hart

We have previously shown that signals sent from skin irradiated with erythema UV to the bone marrow stimulate the development of dendritic cells that are poorly immunogenic and cannot induce a strong immune response. Similar responses have been detected following multiple exposures to sub-erythema UV radiation. 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, were analysed. We studied that metabolism of dendritic cells generated from the bone marrow of UV-irradiated mice. Contrary to our hypothesis, we believe

that the cells differentiated from the bone marrow of UV-irradiated mice versus those from non-irradiated control mice have increased glycolytic activity, with no difference observed in mitochondrial respiratory function. This suggests that metabolism and function of dendritic cells may be linked. Mice were also given the demethylating agent, 5-Aza-2-deoxycytidine, at the time of UV irradiation of skin. As the function of bone marrow-derived dendritic cells was restored in mice given 5-Aza-2-deoxycytidine, we believe that an epigenetic event was involved.

Funded by Asthma Foundation WA, Scott Kirkbride Melanoma Research Foundation

Effect of a short Prostaglandin E2 pulse on bone marrow cells engrafted into chimeric mice

Terry McGonigle, Will Kermode, Naomi Scott, Prue Hart.

Regulatory dendritic cells are generated by culture of bone marrow cells from UV-irradiated mice or mice exposed to subcutaneous pellets releasing prostaglandin E2. To determine whether prostaglandin E2 acts directly on bone marrow cells, or indirectly via an effect on other cells, the outcome of a 60 minute pulse of bone marrow cells with a stabilised derivative of prostaglandin E2, namely 16,16-dimethyl prostaglandin E2 (dmPGE2), was investigated. Dendritic cells differentiating from bone marrow given a dmPGE2-pulse were similarly poor at inducing new



immune responses. Then, to remove the potential artificial effect of bone marrow cell culture, we established chimeric mice with bone marrow cells pulsed with dmPGE2. The efficiency of the engrafted dendritic cells was sought with increasing time after bone marrow cell engraftment (CD45.1 into CD45.2 mice). After 2-3 weeks, the differentiating dendritic cells had poor priming ability but after 16 weeks, this effect was no longer detected. This suggested that the effect of PGE2 may be dose-dependent and reversible. In experiments in which the recipient mice, not the donor mice, were UV-irradiated, no differences were detected and suggested that the effect of PGE2 was direct on haemopoietic progenitors in the bone marrow.

Funded by Asthma Foundation WA, Scott Kirkbride Melanoma Research Foundation, Multiple Sclerosis Research Australia

Effect of experimental allergic airways disease on bone marrow-derived dendritic cells

Naomi Scott, Royce Ng, Terry McGonigle, 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, bone marrow derived dendritic cells are regulatory. Further their development

is blocked by the administration of indomethacin and again suggests that inflammation-induced PGE2 is responsible. We also gave mice the demethylating agent, 5-Aza-2-deoxycytidine, at the time of allergen airways challenge. This removed the effect of inflammation-induced PGE2 on bone marrow-derived dendritic cell function, and suggested the involvement of an epigenetic event. 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 Asthma Foundation WA

The effects of vitamin D deficiency on inflammation and the microbiome of the lungs

Shelley Gorman, Denise Anderson, Claire Weeden, Luke Berry, Vanessa Fear, Martin Feelisch, Sian Geldenhuys, Alex Larcombe, Anthony Kicic, Prue Hart

In 2014 we continued to examine the effects of vitamin D deficiency on lung inflammation, with a new focus on the role of the microbiome. In these studies, we compared the effects of dietary vitamin D with of gestational and neonatal vitamin D deficiency induced by feeding female mice and their offspring a diet deficient in vitamin D. 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 more recent studies, we observed increased inflammation and bacteria levels in the lungs of naïve vitamin D-deficient male mice. 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 Copenhagen) we have used high throughput sequencing to examine how vitamin D deficiency may affect the type of bacterial species that compose the microbiome of the lungs. We are now examining whether changes to the microbiome and 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 Hart, Raelene Endersby, Peter Jacoby, and Shelley Gorman

In 2014 we published our studies investigating the suppressive effects of skin exposure to ultraviolet radiation on the development of signs of obesity and the metabolic syndrome in the leading endocrinology journal,

Diabetes. Exposure to low-dose UVR also had beneficial effects on weight gain, adipose tissue accumulation, glucose intolerance and insulin resistance and other risk factors for the metabolic syndrome in mice fed a high diet. The effects of UV irradiation were independent of any change in vitamin D status. We also demonstrated that some of the UV-related effects on obesity development occurred through a nitric oxide dependent pathways. These studies involved collaborations with British researchers, Professors Richard Weller (University of Edinburgh) and Martin Feelisch (University of Southampton).

Funded by the Brightspark Foundation and the Telethon Kids Institute

Cross-presentation of cutaneous melanoma antigen by migratory XCR1+CD103- and XCR1+CD103+ dendritic cells

Ben Wylie, Elke Seppanen, Kun Xiao, Rachael Zemek, Damien Zanker, Sandro Prato, Bree Foley, Prue H. Hart, Richard A. Kroczek, Weisan Chen and Jason Waithman

The question of which dendritic cells (DCs) cross-present peripheral tumor antigens remains unanswered. We assessed the ability of multiple skin-derived and lymphoid resident DCs to perform this function in a novel orthotopic murine melanoma model where tumor establishment and expansion is within the skin. Two migratory populations defined as CD103-XCR1+ and CD103+XCR1+



efficiently cross-presented melanoma-derived antigen, with the CD103-XCR1+ DCs surprisingly dominating this process. These results are critical for understanding how anti-tumor CD8+ T cell immunity is coordinated to tumor antigens present within the skin.

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

Ben Wylie, Prue Hart and Jason 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

type I interferon enhances the therapeutic efficacy of adoptive T cell therapy

Anthony Buzzai, Vanessa Fear, Willem Lesterhuis, Raelene Endersby, Andreas Behren, Prue Hart and Jason Waithman

Immunity commonly observed during acute viral infection is identical to what we would like to induce and sustain against cancer. Type I interferons (IFN-I) are one of the first cytokines produced during a viral infection and are responsible for directly and indirectly modulating the anti-viral immune response. Thus, it is logical that IFN-I has the potential to enhance anti-tumour immunity. However, systemic administration of IFN-I to melanoma patients has not improved overall

survival. This treatment has been limited to the use of only one subtype, IFN- γ . Considering 13 additional subtypes exist, we asked whether other IFN-I subtypes have an effect against melanoma and if they could be used to increase the efficacy of adoptive T cell therapy.

Funded by NHMRC and UWA
Postgraduate Award to AB

Personalised therapeutic peptide vaccination targeting mutated cancer antigens

Paul Watt, Mark Cruickshank, Justine Mintern, Shane Stone, Timo Lassmann, Raelene Endersby, Anthony Bosco, Alex Gout, Bree Foley, Katrin Hoffmann, Robyn Lucas and Jason Waithman

The paradigm for cancer treatment is evolving from non-specific cytotoxic agents to selective, mechanism-based therapies. A successful example is immunotherapy, with this modality now proving to be an effective adjunct therapy for patients with cancer. Indeed, the journal *Science* recently named cancer immunotherapy 'The 2013 Breakthrough of the Year'. The most promising and effective immune-based therapies harness the activity of helper and killer T cells. The overall aim of this project is to use a novel therapeutic peptide vaccine strategy to generate T cell immunity directed against mutated cancer antigens.

Funded by NHMRC

The role of tissue-resident memory T cells in cutaneous melanoma

Thomas Gebhardt and Jason Waithman

Until recently, it has been widely accepted that memory T cells are a heterogeneous population, comprised of two subsets: central memory (TCM) and effector memory (TEM) CD8 T cells. TCM cells circulate within secondary lymphoid organs, where they lack immediate effector function, instead having the capability to proliferate and differentiate into cytotoxic T cells. TEM cells are excluded from the lymph nodes and unlike TCM cells, have immediate effector functions. Recently, a third subset of memory T cells has been recognised, known as tissue-resident memory T cells (TRM). TRM 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 TRM subset remains resident at the site of pathogen entry, where they can efficiently control secondary challenge. For example, TRM 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 TRM 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,
NHMRC Career Development Fellow

Shelley Gorman BSc (Hons) PhD,
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Robyn Lucas BSc MBCHB MPH&TM
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Terence McGonigle BSc (Hons),
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Postgraduate Students

Ben Wylie (Hons), PhD candidate

Sian Geldenhuys, PhD candidate

Anthony Buzzai (Hons), PhD candidate

Rachel Foong BSc (Hons), PhD
Candidate

Elouise Greenland BSc (Hons), PhD
Candidate, Dept Pharmacology

Simon Ghaly MBBS, FRACP, PhD
Candidate, Dept Medicine

Tenielle George (Hons), PhD candidate

Honours Students

Chelsea Wilson BSc

MSRA Vacation Scholar (10 weeks)

William Kermode

Theses passed

Samantha Winter BSc Honours

Ayesha Dhillon-LaBrooy BSc Honours

Awards

Prue Hart:

NHMRC:

1067209 Narrow band UVB
phototherapy for patients with Clinically
Isolated Syndrome: A phase 1 trial
PH Hart, DR Booth, A Kermode,
D Nolan, R Lucas, W Carroll, J Cole
\$660,558.00 2014-2016

Other:

SEDS: Sun exposure versus vitamin D
supplementation for human health
R Lucas, R Neale, PH Hart,
\$582,911 2013-2015
Cancer Australia

Epigenetic changes to dendritic cell
progenitors in the bone marrow of mice
with inflammatory airways PH
Hart \$26,175 2013-14 Asthma Fdn
WA

A novel immune component of the
susceptibility formula for melanoma
PH Hart

S Gorman \$75,000 2014
Scott Kirkbride Melanoma Foundation

Shelley Gorman:

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).

Department of Health (Western Australia) Merit Award Project Fellowship (2014: \$5,000: Harnessing ultraviolet radiation to curb the development of obesity)

Asthma Foundation of Western Australia Grant (2015: Gorman, Matthews, \$24,821). Exploring the effects of maternal obesity on asthma pathogenesis.

UWA, Faculty of Medicine, Dentistry and Health Science Near Miss Grant (2014: Gorman, Mori, Lucas, Matthews, Siafarikas, Oddy, Jakoby; \$70,000). Could sunlight be harnessed for the control of obesity and metabolic syndrome?

Scott Kirkbride Melanoma Research Centre Priming Grant (2014: Hart, Gorman; \$75,000). A new component of the susceptibility formula for melanoma.

Princess Margaret Hospital Foundation Seed Grant (2014: Oo, Gorman, Le Souef, Zhang \$20,000). Analysis of vitamin D and cathelicidin levels in children with acute asthma exacerbations in relation to viral analysis.

Jason Waithman:

Project Grant: CIA Waithman; "Paediatric brain tumour immunotherapy"; Funding Source: Telethon Adventurers; Duration: 3 years (2015-2017) Amount: \$375,000

Career Development Fellowship Level 1: APP1066869 – "Immunity

to melanoma"; Sole CIA Waithman; Funding Source: NHMRC; Duration: 4 years (2014-2017); Amount: \$404,884

Linkage Infrastructure, Equipment and Facilities Grant: LE150100066 – "A breakthrough in multidimensional systems biology"; PI Waithman; Funding Source: ARC; Duration: 1 year (2014); Amount: \$440,000

Project Grant: APP1052141 – "Induction of adaptive immunity during melanoma"; Sole CIA Waithman; Funding Source: Cancer Australia and Cure Cancer Australia; Duration: 2 years (2013-2015); Amount: \$199,245

Invited Presentations

Prue Hart:

June: Invited speaker, Endocrinology Forum, SCGH, Nedlands

August: Invited speaker, Lung Club, SCGH, Nedlands

Speaker, Raine meeting.

September: International Photobiology Congress, Cordoba, Argentina, Invited Symposium speaker (free registration)

October: Invited speaker, National SKMRF Melanoma Conference, Perth

November: Invited symposium speaker, MEPSA/AHMRC, Melbourne

Invited speaker, Endocrinology symposium for M Maclean from Westmead Hospital

Shelley Gorman:



The Inaugural Developmental Origins of Health and Disease Society of Australia and New Zealand Meeting (Perth, April 2014). Does vitamin D really have any role in autoimmunity or allergy?

The Annual Scientific Meeting of the Australian Endocrine Society (Melbourne, August 2014). Tissue-specific effects: Vitamin D action in the immune system.

Jason Waithman:

Invited national speaker: Cure Cancer Australia Researcher Symposium (2014)

Invited national seminar: Melanoma WA (2014), Perth Cancer Club (2014)

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, Adelaide, May 2015.

Shelley Gorman:

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

LUNG GROWTH AND RESPIRATORY ENVIRONMENTAL HEALTH

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: Prof Steve Stick, PMH; Prof Peter Sly, UQ, Prof Barry Marshall, UWA) and environmental exposure studies (Collaborators: Dr Peter Franklin, WA Department of Health, 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, Telethon Kids Institute) 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 hyper-responsiveness in obstructive disease. These studies are largely driven by A/Prof 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).

Early life determinants of lung growth

Vitamin D deficiency and lung growth

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

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 link 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 published work showing 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. She has also found that in utero vitamin D deficiency was sufficient to alter lung structure and function and differentially regulate genes important in lung development. Finally, she has also demonstrated in a mouse model of chronic allergic asthma that vitamin D can modulate asthma-related genes and contribute to asthma symptoms. Rachel will include this work in her PhD thesis, which will be submitted in 2015.

Funding: NHMRC Project Grant (2013-2015).

Respiratory environmental health

Environmental health of remote Aboriginal communities

Holly Clifford, Graeme Zosky (University of Tasmania), 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 specific effects of dust on the cells of the human airway, and to investigate how dust exposure contributes to the severity of common bacterial infections seen in Aboriginal children.

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

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 intranasal instillation of DEP (ie small amounts of DEP in solution are placed on the nose of mice and inhaled). We followed this by establishing a more realistic mouse model of whole diesel exhaust exposure by exposing mice to exhaust generated by a Euro 1 diesel engine under partial load. 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. These data were published in 2014 in *Inhalation Toxicology*.

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 published in 2014 in *Environmental Toxicology*.

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

The respiratory health effects of electronic cigarettes

Alexander Larcombe, Peter Franklin (Department of Health, Western Australia), Ben Mullins (Curtin)

Electronic cigarettes (“e-cigarettes”) heat and atomize a liquid solution (“e-juice”) producing an aerosol which is inhaled. They are a very new technology and their use is widespread and increasing rapidly especially in adolescents. In many countries, the number of people regularly using e-cigarettes is doubling annually, and there are an estimated 200,000 current Australian users. Despite this, the potential for e-cigarette use to impact health is virtually unknown. This knowledge gap has been recognized as a research priority by international medical associations and it is this knowledge gap that our proposed research aims to help fill. The limited data on e-cigarettes that exist suggest that: (i) they are likely to have a negative



impact on health, especially in situations of pre-existing respiratory disease, (ii) pregnant women are more likely to use them compared with conventional cigarettes and (iii) the type of e-cigarette e-juice can significantly influence health outcomes. In Australia, the laws surrounding the importation, sale and use of e-cigarettes are vague, and hard-data on their potential to impact health are urgently required to guide policy makers.

In 2014 we received Department of Health, Western Australia funding to perform the first study investigating the long term respiratory health effects of electronic cigarette vapour exposure. We employed our expertise in pre-clinical exposure models to expose mice to either tobacco smoke, medical air (control) or one of 4 different types of e-cigarette vapour from week 4 to week 12 of life. E-cigarette vapours varied depending on nicotine content (0 or 12mg/mL) and the main excipient (propylene glycol or vegetable glycerin). We then measured lung volume, lung mechanics, responsiveness to methacholine and pulmonary inflammation. Mice exposed to tobacco cigarette smoke showed increased pulmonary inflammation and responsiveness to methacholine, compared to air controls. Mice exposed to e-cigarette vapour did not have increased inflammation, but did display decrements in parenchymal lung function at both functional residual capacity and high transrespiratory pressures. Mice exposed to vegetable glycerin based e-cigarette vapours

were also hyper-responsive to methacholine (similar to tobacco smoke exposed mice) regardless of the presence or absence of nicotine. This study shows, for the first time, that chronic exposure to e-cigarette vapour is not harmless to the lungs, and results in significant impairments in lung function. They also indicate that the e-cigarette excipient used is important, with the most severe impairments seen in mice exposed to vegetable glycerin based vapour. Our results suggest that caution should be exercised when advocating e-cigarettes as a safe alternative to tobacco smoking, and that further research in this field is warranted.

In 2014 we also received an Asthma Foundation of Western Australia Project Grant to study the potential for e-cigarettes to exacerbate asthma. These studies are ongoing.

Funding: Asthma Foundation of Western Australia, Department of Health, Western Australia.

Mechanisms of airway hyperresponsiveness in asthma

Viral induced airway hyperresponsiveness

Alexander Larcombe, Jennifer Phan, Rachel Foong, Anthony Kicic, Steve Stick, Peter Sly, Peter Noble (UWA), Graeme Zosky (University of Tasmania)

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 hyperresponsiveness (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 and 2013 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. We infected mice with HRV in early life 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 published in PLoS One in 2014. 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. Our manuscript on this topic is currently under review.

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 characterised 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 TGF α 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.

In 2014, we have combined this non-inflammatory transgenic mouse model of ASM remodelling with an established allergic mouse model. We found that allergic inflammation does not enhance airway hyperresponsiveness produced by thickening of the ASM layer. Findings bring into the question the perceived causal relationship between allergy and remodelling which may instead be independent features of asthma.

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.

In August 2014, we managed to secure the Asthma Foundation Western Australia New Investigator Grant to fund this study. We will be increasing the sample size of this study in 2015.

Staff and Students

Head of Group

Alexander Larcombe PhD

Senior Research Fellow, Telethon Kids Institute

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

Research Team

Holly Clifford PhD

Research Officer, Telethon Kids Institute

Lecturer, Centre for Child Health

Research, The University of Western Australia

Kimberley Wang PhD

Research Officer, Telethon Kids Institute

Lecturer, Centre for Child Health Research, The University of Western Australia

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Lecturer, University of Tasmania (Honorary member)

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Laboratory Manager, Telethon Kids Institute

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Research Assistant

Rachel Foong BSc(Hons)

Part-time Research Assistant, Telethon Kids Institute

Postgraduate Students

Rachel Foong BSc(Hons) PhD
Candidate

Research Support

Ms Marina Stubbs, Administration
Officer

Awards

Alexander Larcombe - Telethon-Perth
Children's Hospital Research Fund 2013

(Round 2) \$217,000

Alexander Larcombe - Department of Health, Western Australia \$49,000

Alexander Larcombe - Australasian Society of Clinical Immunology and Allergy (ASCIA) Annual Conference Best Poster (Allergy)

Alexander Larcombe - TSANZ Annual Meeting, Occupational and Environmental Lung Disease Best Presentation

Alexander Larcombe - TSANZ Janet Elder International Travel Award

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

Kimberley Wang – TSANZ Travel Grant - \$540.

Kimberley Wang – Barbara May Scholarship, Telethon Kids Institute - \$4,900.

Holly Clifford - The Raine Foundation Priming Grant \$200,000

Holly Clifford - Robert Pierce Grant-in-Aid for Indigenous Lung Health Award \$15,000

Holly Clifford - TSANZ/Japanese Respiratory Society Early Career Development Award

Rachel Foong - Perron Performance Award

Rachel Foong - Asthma Foundation of Western Australia PhD Scholarship Top-Up

External Committees

National

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

Alexander Larcombe – Rebecca L Cooper Medical Research Foundation Scientific Review Committee

Local

Holly Clifford - 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

Alexander Larcombe - Curtin Health Innovation Research Institute, Perth, July 2014. "Biodiesel Exhaust – the Need for Health Effects Research".

Alexander Larcombe - Thoracic Society of Australia and New Zealand, Western Australia Branch Annual Meeting. Perth, July 2014. "Biodiesel Exhaust – the Need for Health Effects Research".

Alexander Larcombe - University of Western Australia - School of Anatomy, Physiology and Human Biology, Perth, May 2014. "Ventilation systems - how to make a decent gas exchange system".

Alexander Larcombe - Ondek Pty Ltd. Perth, February 2014. "Measuring Lung Function and AHR in Mice ...and results to date".

Western Australia

ACTIVE collaborations

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

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

Prof Peter Richmond/Dr Ruth Thornton, University of Western Australia

Dr Peter Franklin, Department of Health,

ORIGINS PROJECT

ORIGINS is a new birth cohort study, based upon the Developmental Origins of Health and Disease (DOHaD) hypothesis: preventive intervention strategies are best targeted in early life. The Project is the result of strong expertise and experience in the DOHaD Field in WA, an initiative led by UWA and the Telethon Kids Institute. The Project is designed to collect detailed information about how the early environment influences the risk of a broad range of early and later onset diseases including asthma, allergies, diabetes, obesity, renal disease, mental health disorders and their many complications. We will recruit women (and the father of their baby) early in pregnancy and collect data on their health, diet, physical activity patterns and a range of factors in their environment. We will then assess how these early life exposures influence their child's growth, development, and health (including neurodevelopment, evidence of allergies, infections, and other medical history).

The greatest potential for improving future health lies in early intervention and there is already substantial evidence that initiatives to promote a 'healthy start to life' can reduce the risk of both early and later non-communicable diseases with wide social and economic benefits.

The Project is grounded in making meaningful changes that will reduce the risk of common health conditions. Interventions to improve modifiable aspects of the early life environment

(such as nutrition, physical activity, sleep, time spent indoors and outdoors, smoking and pollutants, microbial diversity, water, air and food quality) are the most logical, large scale and effective long-term strategies to improve all aspects of physical and psychological wellbeing, both in childhood and in later life. Nested within the main observational cohort will be a series of intervention studies. Building upon the success of the Raine Study, this new birth cohort will have detailed data and sample collection, including detailed environmental and biological profiling using cutting edge technologies such as metagenomics, immune profiling, metabolomics, and genomics.

The ORIGINS Project encompasses a wide engagement of clinicians, researchers, and the community. We have collaborations with other national and international longitudinal studies, ensuring harmonisation of research methods. ORIGINS is a large collaboration of clinical disciplines, all focused on taking a more integrated approach from the outset to ensure optimal capacity and inbuilt interventions through translational research.

ORIGINS is a new birth cohort study, designed to collect detailed information about how the early environment influences the risk of a broad range of early and later onset diseases including asthma, allergies, diabetes, obesity, renal disease, mental health disorders and their many complications.

We will recruit women (and the father of their baby) early in pregnancy and collect data on their health, diet, physical activity patterns and a range of factors in their environment. We will then assess how these early life exposures influence their child's growth, development, and health (including neurodevelopment, evidence of allergies, infections, and other medical history).

Funders: Joondalup Health Campus,
Telethon Kids Institute

PAEDIATRIC RESPIRATORY PHYSIOLOGY

The Paediatric Respiratory Physiology research group was established in mid 2010 with the appointment of Prof Graham Hall by the Telethon Kids Institute. 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 disease

Investigators: Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Kathryn Ramsey, Caroline Gallagher, Jasmine Grdosic, Tim Rosenow and Rachel Foong 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

Long term outcomes of infant lung function in cystic fibrosis

Investigators: Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Kathryn Ramsey, Caroline Gallagher, Tim Rosenow and Rachel Foong as part of the AREST CF collaboration (www.arestcf.org)

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

Investigators: Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Kathryn Ramsey, Caroline Gallagher and Rachel Foong as part of the AREST CF collaboration (www.arestcf.org)

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

Investigators: 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

Preterm birth and Bronchopulmonary dysplasia

Bronchopulmonary Dysplasia: Identifying Cardiorespiratory Consequences and Targets for Prevention and Intervention.

Investigators: Jane Pillow, Graham Hall, Andrew Wilson, Zoltan Hantos, Shannon Simpson, Andrew Gill, Naomi Hemy,



Nada Townsi

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of preterm birth and the most common form of chronic lung disease in infancy. Although BPD is often assessed in relation to the lung alone, the clinical picture is more of a complex multisystem disorder with multiple antecedent contributory factors and extrapulmonary manifestations including abnormal cardiac, pulmonary vascular, chest wall and respiratory muscle development as well as neurodevelopmental impairment. There are few data to indicate the frequency or severity of abnormal cardiac, pulmonary vascular, chest wall and respiratory muscle outcomes after very preterm birth, and their contributions to respiratory problems in very preterm infants are unknown.

We will approach BPD as a clinical disorder resulting from abnormal function of the integrated thoracic unit. We will quantify contributions of cardiovascular, respiratory muscular and pulmonary contributions to the development and persistence of the new BPD clinical phenotype in a large (n=500) regional cohort of very preterm infants by performing comprehensive lung, cardiac and diaphragmatic function testing prior to initial hospital discharge and again at 12 months. Risk indices for perinatal adverse exposures and abnormal function of each system will be used to develop a predictive model for moderately severe BPD. The identification of a significant incidence

of cardiovascular, chest wall or respiratory muscle contributions to BPD will provide novel data that will inform planning for health service delivery including identification of infants at high risk who may benefit from early intervention, and development of guidelines for additional screening and monitoring of extrapulmonary disease.

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

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

Investigators: 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 approach to the treatment and management of infants with BPD through the neonatal period and into childhood.

Key outcomes include

- Nearly all preterm children have abnormal lung structure, irrespective of the presence of BPD. More structural abnormalities on chest CT are associated with lower lung function in preterm children at 9-12 years of age.
- 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

Investigators: 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 CH 7

Telethon Trust

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 adolescents 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 now complete. We have already identified

several risk factors for persistent and later-onset asthma in the cohort, and found that some asthma diagnosis tests do not work as well as current literature would suggest in community groups.

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

Investigators: Prof Graham Hall, Dr Shannon Simpson, Prof Stephen Stick, Dr Afaf Albloushi and Ms Georgia Banton Mr Mark Kendall

Summary: 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 exercise 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

Investigators: 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 anaesthesia, 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 surgery 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

Prediction and prevention of peri-operative respiratory adverse events (PRAE)

Obesity: the mechanics of lung function impairment and risks related to PRAE

Background: In paediatric anaesthesia obesity is a significant problem with obese children not only having anaesthesia-relevant co-existing diseases like asthma or hypertension, but also having a higher incidence of anaesthesia related complications. Perioperative Respiratory Adverse Events (PRAE) are amongst the most common complications observed in this population and a previous observational study has demonstrated an increased likelihood of these events occurring in these children. Many factors encountered during

GROUP NAME

general anaesthesia such as supine positioning (lying down, face up), anaesthetic agents and the type of surgery affect the functioning of the respiratory system and in particular lung volumes and respiratory mechanics. These anaesthesia related changes in lung function are expected to be even more significant in obese patients. Since PRAE remains the main cause of perioperative morbidity, especially in this population, a better knowledge of both the changes in lung function caused by anaesthesia and the impairment of the respiratory mechanics by obesity will help to improve the management of this high risk category of patients. This study thus aims at assessing the lung function changes as well as the incidence of PRAE in healthy and overweight/obese children with an expectation that the incidence of PRAE will be higher in the obese/overweight children. The state of consciousness and body position is expected to affect the functional residual capacity while respiratory resistance is expected to be significantly higher in the overweight/obese children too.

Normal values of lung resistance; an evidence-based guideline for paediatric anaesthesia

Background: Paediatric patients undergoing elective or emergency surgery, or who have been admitted to the Neonatal/Paediatric Intensive Care Unit (NICU/PICU), often require mechanical ventilation. During the perioperative period, these patients are at risk of several types of lung

injury, including atelectasis (collapse of lung tissue), pneumonia (disease marked by inflammation of the lungs), pneumothorax (presence of air within the pleural cavity leading to lung collapse), Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Anaesthetic management can contribute to these injuries, exacerbate any underlying lung conditions or even improve outcomes, depending on the specific situation. Moreover, several studies have shown that pulmonary complications, more specifically respiratory failure requiring ventilation, are associated with high morbidity and mortality along with increased health-related costs and greater length of hospital stay. Ventilation mode (volume, pressure or dual), modality (controlled, assisted, support ventilation) and respiratory parameters (e.g. tidal volume and respiratory rate) are the most important factors of mechanical ventilation. An important aspect of ventilation strategies is to optimise respiratory mechanics. A critical part of this process is knowing the normal range of respiratory mechanics during ventilation. This allows clinicians to define ventilation such that the respiratory mechanics can be maintained at a level expected for that particular patient and therefore protect against over- or under ventilation and thus minimise potential harm. While the normal ranges of a variety of respiratory outcomes during mechanical ventilation have been assessed in adults, there are no normal reference ranges of values available for the paediatric population.

This precludes the formulation of clear evidence-based ventilation guidelines in children. We are thus aiming at collecting lung function outcomes (respiratory resistance and pulmonary compliance) in healthy children aged between 1 and 15 years old undergoing surgery under general anaesthesia and requiring mechanical ventilation. The data and demographic information collected will then be used to develop robust prediction equations and nomograms that define the values of physiological parameters to be programmed in the mechanical ventilators for optimal lung function in anaesthetised children having surgery.

Clinical

Collation of multi centre plethysmographic lung volumes data to derive reference equations for Caucasian children.

Investigators: 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 healthy 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 range of static lung volume outcomes.

Assessing the accuracy of the hypoxia challenge test to predict in-flight hypoxia in infants

Investigators: Graham Hall, Maureen Verheggen, Evelyn Low, Wendy Lim and Lisa Chau

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 Rachel Foong – Research Officer

Ms Caroline Gallagher – Research Assistant

Ms Naomi Hemy - Research Assistant

Mr Chris O’Dea B. Med Sci (Resp Hsci) Hons – Senior Respiratory Scientist

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 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 - MHIItSci, CRFS.

Ms Jasmine Grdosic – Honours Student

Mr Mark Kendall – Honours Student

Evelyn Low, Wendy Lim and Lisa Chau

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

Kathryn Ramsey

NHMRC CJ Martin Early Career Biomedical Fellowship

Vertex Cystic Fibrosis Research Award

North American Cystic Fibrosis Conference Young Investigator Award

Dr Louisa Alessandri Memorial Fund Prize for Scientific Publication

Shannon Simpson

Thoracic Society of Australia and New Zealand Janet Elder Award

TSANZ Travel Award; Awarded to attend the annual scientific meeting

External Committees

International

Graham Hall

- Joint American Thoracic Society - European Respiratory Society Working Party on Infant Lung Function Testing (2003-Ongoing)
- 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
- Editorial Advisory Panel; Expert Review of Respiratory Medicine (Oct 2006 – Ongoing)
- Secretary; Paediatric Respiratory Physiology Group, European Respiratory Society (Sep 2012 – Ongoing)
- Jan 2014 – Ongoing Series Editor; Respirology
- May 2014 ERS 2014 Paediatric Respiratory Physiology Abstract review committee
- Oct 2014 – Ongoing ERS College of Experts

Kathryn Ramsey

- Joint American Thoracic Society – European Respiratory Society Working Group for the Standardisation of Inert Gas Washout Technique (2013 - ongoing)

National

Graham Hall

Member Medical and scientific advisory committee, Asthma Australia (2013 –)

Andrew Wilson

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

GROUP NAME

2013-2014 Telethon Kids Leadership course member

Invited Presentations

Graham Hall

- Joint ANZSRS and TSANZ: Laboratory Accreditation workshop
- TSANZ: “Oxygen Therapy Symposium: Oxygen therapy in Children”
- Joint WA TSANZ and ANZSRS Annual scientific meeting: The global challenge of reference ranges: The new Global Lung Function Initiative equations.
- Joint New Zealand TSANZ and ANZSRS annual meeting: “Normal Perturbations in respiratory physiology at rest”
- Joint New Zealand TSANZ and ANZSRS annual meeting: “Laying the foundations in childhood for healthy or disease adult lungs”
- Hong Kong Society of Paediatric Respiriology: Lung Function Workshop “Lung function testing in children”
- Hong Kong Society of Paediatric Respiriology: “Using measurements of respiratory resistance in clinical paediatric respiratory medicine”
- Asthma Foundation WA, World Asthma Day Symposium: “Making spirometry work for you”

Shannon Simpson

TSANZ 2014 (Adelaide) Talk

“Lung function decline in school-age children with a neonatal classification of bronchopulmonary dysplasia (BPD)”

Tim Rosenow

PRAGMA: a new method of quantifying structural lung disease in young children with cystic fibrosis. Thoracic Society of Australia and New Zealand, Adelaide, South Australia.

PRAGMA: Further support for use as a quantitative CT outcome measure. 28th Annual North American Cystic Fibrosis Conference, Atlanta, USA.

A new gold standard for assessing CT in early CF lung disease? European Respiratory Society International Conference, Munich, Germany.

TSANZ Cystic Fibrosis SIG Prize

Anoop Ramgolan

2014: Thoracic Society of Australia and New Zealand, WA scientific meeting

Presentations :

- Can exhaled nitric oxide be used to predict children at higher risk of perioperative respiratory adverse events.
 - Salbutamol – does it go where we want it to?
- 2014: Child and Adolescent Health Symposium
- Can exhaled nitric oxide be used to predict children at higher risk

of perioperative respiratory adverse events

- Can't intubate can't oxygenate scenario – rabbits II
- Can't intubate can't oxygenate scenario – rabbit III

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

Alcohol & Pregnancy & FASD Research

Fetal Alcohol Spectrum Disorders (FASD) are preventable and our research will reduce the risks and effects of prenatal alcohol on child health through prevention, diagnosis and therapy interventions.

FASD are characterised by brain damage from prenatal alcohol exposure and the effects are lifelong. Resultant neurodevelopmental disabilities include developmental delay, poor executive functioning, and problems with learning, behaviour, and social and adaptive functioning. These can lead to secondary outcomes such as poor school performance, unemployment, substance abuse, mental health problems and justice system engagement. Without intervention this may lead to a cycle of welfare dependency and privation which has significant intergenerational social and economic impact. For example, Fetal Alcohol Syndrome has been calculated at \$USD5bn per annum, with a lifetime cost for individuals ranging from \$USD1.6m to \$2.5m.

The Alcohol & Pregnancy & FASD Research Group has led research and policy development in the area of FASD for over a decade, has influenced policy and practice across a range of health professions and has engaged with consumers in the research process. Together with inquiries and plans calling for action, there is strong support from advocacy groups and professions

in health, justice and education for implementation of strategies for prevention and for managing children and young people with FASD. Aboriginal communities have been at the forefront of these calls and have been proactive in seeking strategies to address educational and employment potential, and cultural integrity which is threatened by the learning and behavioural consequences of FASD.

Our current program of research encompasses the following projects:

Epidemiology of FASD in WA – prevalence rates using data from the WA Register of Developmental Anomalies

Investigators: Raewyn Mutch, Rochelle Watkins, Carol Bower

Telethon Kids Institute, The University of Western Australia, Perth, Australia

Data on notified cases of FASD born in Western Australia 1980 – 2010 were identified from the WA Register of Developmental Anomalies. Tabulated denominator data were obtained from the Midwives Notification System. Prevalence rates per 1000 births were calculated by demographic variables. Prevalence ratios (PRs) and 95% confidence intervals (Cis) of Aboriginal compared with non-Aboriginal prevalence rates were calculated. PRs were also calculated to compare rates for births 2000 – 2010 with 1980 – 1989.

210 cases of FASD were identified: a birth prevalence of 0.26/1000 births

(95% CI 0.23-0.30). The majority of cases reported were Aboriginal (89.5%), a rate of 4.08/1,000, compared with 0.03/1,000 in notified non-Aboriginal cases, giving a PR of 139 (95% CI 89-215). The prevalence of FASD in 2000 – 2010 was over twice that in 1980 – 1989 for both Aboriginal (PR 2.37, CI 1.60-3.51) and non-Aboriginal (PR 2.13, CI 0.68-6.69) children. Population surveillance data such as these are valuable in advocating for and monitoring the effectiveness of preventive activities and diagnostic and management services.

Findings from this study have been published in: Mutch RC, Watkins R, Bower C. Fetal alcohol spectrum disorders: Notifications to the Western Australian Register of Developmental Anomalies. *Journal of Paediatrics and Child Health*. 2014. doi:10.1111/jpc.12746

Funding: This project was supported by the NHMRC Program Grant 572742 and Research Fellowship 634341

Health and adverse life outcomes among individuals notified with FAS in Western Australia: implications for policy, service delivery and prevention

Investigators: Rochelle Watkins, Carol Bower

Telethon Kids Institute, The University of Western Australia, Perth, Australia

A retrospective population-based study of FAS diagnoses in WA will be conducted to describe health and adverse life outcomes, and

health service use, among notified Fetal Alcohol Syndrome (FAS) cases, including emergency department encounters, hospital admissions, intellectual disability, contact with mental health services, school performance, and interactions with the WA criminal justice system. Health and adverse life outcomes among individuals with FAS will be compared with a population based comparison group. Comparative analysis of outcomes among individuals with FAS and those in the comparison group will enable identification of the population-level attributable risk for adverse life outcomes associated with FAS. A health economic analysis will also be undertaken.

Funding: Foundation for Alcohol Research and Education

Prenatal alcohol use & educational outcomes

Investigators: Carol Bower, Steve Zubrick

Project staff: Kirsten Hancock¹, Nadia Cunningham

Telethon Kids Institute, The University of Western Australia, Perth, Australia

In this project, we are using linked data to examine the educational outcomes for children of women with a record of an alcohol-related condition in the hospital morbidity data system, compared with the educational outcomes of children of women with no such record.

Funding: ARC Grant DP140101573 and

Research Fellowship 634341

Alcohol and pregnancy and fetal alcohol spectrum disorder: Midwives' knowledge, attitudes and practice

Investigators: Jan Payne¹, Rochelle Watkins¹, Heather Jones¹, Tracy Reibel¹, Raewyn Mutch^{1,2}, Amanda Wilkins^{1,2}, Julie Whitlock¹, Carol Bower¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

²WA Government Department of Health, Child and Adolescent Health Services, Perth, Australia

This cross sectional study was conducted at 19 maternity sites across the seven health regions of WA. A questionnaire was designed following a review of the literature and other relevant surveys. Midwifery managers of the maternity sites distributed the questionnaires to all midwives working in their line of management. A total of 334 midwives were invited to participate in the research and 73.4% of these were eligible.

The response rate was 67.8%. Nearly all the midwives (93.2%) asked pregnant women about their alcohol consumption during pregnancy and 99.4% offered advice about alcohol consumption in accordance with the Australian Alcohol Guideline, which states "For women who are pregnant or planning a pregnancy, not drinking is the safest option." While informing women about the effects of alcohol consumption in pregnancy (64.2%), they did not always use the recommended AUDIT

screening tool (47.5%) or conduct brief interventions when indicated (70.4%). Most midwives endorsed professional development about screening tools (93.5%) and brief interventions (92.9%). These findings support the need for further professional development and support for midwives.

Findings from this study have been published in: Payne JM, Watkins RE, Jones HM, Reibel T, Mutch R, Wilkins A, Whitlock J, Bower C. Midwives' knowledge, attitudes and practice about alcohol exposure and at risk of fetal alcohol spectrum disorder. *BMC Pregnancy and Childbirth* 2014, 14:377

Funding: This project was supported by the NHMRC Program Grant 572742 and Research Fellowship 634341

3M FASD Prevention Project: Marulu, Mass Media, Midwives

Investigators: James Fitzpatrick¹, Rochelle Watkins¹, Carol Bower¹, Glenn Pearson¹, Jonathan Carapetis¹, Mike Daube², Kaashifah Bruce¹, Elizabeth Chester¹

Project staff: Kaashifah Bruce¹, Martyn Symons¹, Tracy Reibel¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia,

² McCusker Centre for Action on Alcohol and Youth, Curtin University, Perth, Australia.

The objective of the 3M FASD Prevention Strategy is to implement and evaluate a community designed FASD prevention strategy for the Fitzroy

Valley and surrounding communities that if effective can be translated to other settings in Western Australia. This overarching Strategy comprises three distinct but interrelated initiatives responding to high FASD prevalence rates in Western Australia through a whole of community prevention strategy: Marulu, Midwives and Mass Media.

Marulu: An exemplar high-impact FASD prevention strategy in the communities of the Fitzroy Valley, where high FASD prevalence has been documented;

Midwives: A workforce intervention up-skilling midwives in the documentation and brief intervention around alcohol use in pregnancy, to reinforce the community-wide interventions; and
Mass Media: A mass media strategy targeting regional and remote communities throughout the Kimberley and Pilbara, with a further aim of ensuring state-wide impact for the program and its messages.

Local impacts among the Fitzroy Valley communities include an increased knowledge of the harms of drinking while pregnant, altered social norms about the acceptability of drinking while pregnant, and reduced rates of alcohol use in pregnancy and FASD. The social, health and justice system benefits for the Fitzroy Valley communities will be significant and enduring. Documenting the Marulu strategy as an exemplar of a community-initiated response to a significant public health issue will enable this approach to be adopted in other communities in Western Australia

where high-risk drinking is prevalent.

At the regional level across the Kimberley and Pilbara, the media campaigns will raise awareness of the NHMRC guidelines relating to alcohol use in pregnancy. Complementary communication strategies will seek to ensure a further state-wide impact. Additionally, health workforce benefits will be significant in that the AUDIT-C (a screening tool for alcohol use in pregnancy) intervention will have been developed. Training resources will be developed for the implementation of this intervention throughout other communities in regional and metropolitan Western Australia.

Funding: WA Department of Health

Marulu FASD Prevention Strategy

Investigators: James Fitzpatrick¹, Maureen Carter², June Oscar³, Glenn Pearson¹, Jonathan Carapetis¹, Carol Bower¹, Rochelle Watkins¹, Kaashifah Bruce¹

Project staff: Kaashifah Bruce¹, Martyn Symons¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

²Nindilingarri Cultural Health Services, Fitzroy Crossing, Australia

³Marninwarntikura Fitzroy Women's Resource Centre, Fitzroy Crossing, Australia

There is a humanitarian crisis in the Fitzroy Valley region of remote North-western Australia, which has amongst the highest rates of Fetal Alcohol



Spectrum Disorders (FASD) in the world. However, Fitzroy Valley communities have shown strong leadership and commitment to tackling FASD through the initiation of a comprehensive and multifaceted program: the Marulu FASD Strategy that has the bold goal to “Make FASD History” by driving down rates of drinking in pregnancy.

‘Marulu’, meaning ‘precious, worth nurturing’ in the Bunuba language, has three priorities: to prevent FASD, to diagnose FASD and to support affected families. The initial phase of the Marulu FASD Strategy (2008-2013), saw the establishment of a locally-led governance structure, the successful implementation of alcohol restrictions (University of Notre Dame, 2010), and the collection of FASD prevalence data through the Lirilwan Study (Fitzpatrick et al. 2012).

Now, the Telethon Kids Institute has been invited by the communities in the Fitzroy Valley to partner with them in developing, implementing and evaluating a prevention arm of the Marulu FASD Strategy.

Aim:

To develop, implement and evaluate The Marulu FASD Prevention Strategy to increase the proportion of women abstaining from alcohol while pregnant in the Fitzroy Valley.

Objectives:

To work with local health promotion organisations (Nindilingarri Cultural Health Services) to develop and implement a model for Fetal Alcohol

Spectrum Disorder prevention that:

1. Works in the Fitzroy Valley.
2. Can be adapted for FASD prevention in other communities.

This project will develop a model for FASD prevention that can be transferred to other sites. The development of transferable interventions and strategies is also a priority for the community.

Funding: WA Department of Health WA, WA Department of Aboriginal Affairs, McCusker Charitable Foundation

Multidisciplinary Team (MDT) Evaluation: Evaluating multidisciplinary team-based early intervention for children with complex needs, in a remote community setting

Investigators: James Fitzpatrick¹, Maureen Carter², Catherine Elliot^{3,4}, Kaashifah Bruce¹

Project staff: Gayle Segar², Martyn Symons¹, Kaashifah Bruce¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

²Nindilingarri Cultural Health Services, Fitzroy Crossing, Australia

³Chair of Allied Health, Western Australian Child and Adolescent Health Services, WA Health, Perth, Australia

⁴Princess Margaret Hospital for Children Department of Paediatric Rehabilitation

This project aims to evaluate the effectiveness of a multi-disciplinary

team (MDT) model in improving health and developmental outcomes in a cohort of children with complex health needs residing in the Fitzroy Valley, West Kimberley; and to document of the experience and perceptions of families who participate in the MDT model.

Objectives:

- The primary objective of this research project is to develop an effective model for delivering health care services to children with complex needs in remote Indigenous Australia.
- The secondary objective is to deliver the MDT model in a manner that engages local people and families in the health and education support networks established for the benefit of their children.
- The outcomes of this research will benefit the Fitzroy Valley communities by improving the effectiveness of health services to children in their region, and in the longer term, improving the health and education outcomes of these children. A more effective health service delivery model will be of value to families, by providing evidence-based therapy that is coordinated and outcome focused, relative to standard care currently available in the Fitzroy Valley. By including families in the MDT model, the treatment and language relating to their child's health will be de-mystified. This will build families' confidence to engage more proactively with the health and

education services in the future.

Finally, the research will have national relevance by measuring and documenting a best practice approach to delivering child health services in remote Indigenous contexts.

Funding: CAGES Foundation, Royalties for Regions WA

Evaluating the evidence-practice gap between the NHMRC alcohol and breastfeeding guideline (2009), clinician application and maternal uptake

Investigator: Roslyn Giglia

Telethon Kids Institute, The University of Western Australia, Perth, Australia

Alcohol consumption is the cultural norm in Australia but alcohol in breast milk will disrupt the hormonal milieu required for successful lactation and result in a lower milk yield by the baby, a factor rarely considered in the early cessation of breastfeeding. In 2009 the NHMRC released the revised alcohol guidelines and a national first was the inclusion of a guideline exclusively for breastfeeding women (4B)(http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ds10-alcohol.pdf). With limited promotion of this guideline it is not known whether maternal health practitioners such as GPs and midwives, educate women on this guideline in their daily practice. It is also not known whether breastfeeding women are practising safe alcohol consumption during lactation. Given the proven, but not well-known negative

impact of alcohol on breastfeeding, and the importance of extending the positive short (e.g. immunity) and long term effects (e.g. decrease in cancer, diabetes and adult obesity) of breastfeeding, it is important that the awareness and utilisation of this guideline be evaluated.

Dr Roslyn Giglia was successful in being awarded a Translational Research Into Practice (TRIP) Fellowship which will support her to conduct the evaluation of guideline 4B. Building on her PhD research, Dr Giglia has found that anecdotally there is little awareness of guideline 4B or of the adverse effect of alcohol on breastfeeding. The translation of the evaluation of guideline 4B into a practical and targeted awareness raising and education campaign for practitioners and women of child bearing age is not supported by the TRIP Fellowship. Potentially the promotion and uptake of this public policy guideline has the capacity to promote long term breastfeeding which in turn translates into a decrease in infant illness and the prevention of adult chronic diseases.

Funding: NHMRC Translational Research Into Practice (TRIP) Fellowship

Development of a diagnostic instrument for FASD in Australia

Investigators: Carol Bower¹, Elizabeth Elliott^{2,3}, Rochelle Watkins¹, Jan Payne¹, Raewyn Mutch^{1,4}, Amanda Wilkins^{1,4}, James Fitzpatrick¹, Jane Latimer⁵, Sue Miers⁶, Elizabeth Peadon², Anne McKenzie¹, Heather D'Antoine⁷,

Elizabeth Russell⁸, Colleen O'Leary⁹, Jane Halliday¹⁰, Lucinda Burns¹¹, Lorian Hayes¹², Maureen Carter¹³

Project staff: Heather Jones¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

²Discipline of Paediatrics and Child Health, Sydney Medical School, University of Sydney, Sydney Australia

³The Children's Hospital at Westmead, Sydney, Australia

⁴WA Government Department of Health, Child and Adolescent Health Services, Perth, Australia

⁵The George Institute for Global Health, Sydney Medical School, University of Sydney, Sydney, Australia

⁶National Organisation for Fetal Alcohol Spectrum Disorders, Australia

⁷Menzies School of Health Research, Charles Darwin University, Darwin, Australia

⁸Russell Family Fetal Alcohol Disorders Association, Australia

⁹Centre for Population Health Research, Curtin University, Perth, Australia

¹⁰Public Health Genetics, Genetic Disorders, Murdoch Children's Research Institute, Melbourne, Australia

¹¹National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia

¹²Centre for Chronic Disease, School of Medicine, University of Queensland, Brisbane, Australia

¹³Nindilingarri Cultural Health Services, Fitzroy Crossing, Australia

The Australian FASD Diagnostic Instrument was developed to facilitate and standardise the identification of FASD in Australia. This guide provides clinicians with the background information needed to apply standard national diagnostic criteria for FASD in the Australian context. The recommended clinical diagnostic assessment methods are based on the University of Washington (UW) 4-Digit Diagnostic Code¹ method of interdisciplinary team assessment, and the Australian diagnostic categories and criteria combine elements of the UW and Canadian Guidelines for the diagnosis of FASD.² Although the actual 4-Digit Diagnostic Code does not need to be routinely derived during the diagnostic assessment, it can be derived from information recorded on the Australian FASD Diagnostic Assessment Form.

The diagnosis of FASD is complex, and ideally requires an interdisciplinary team of clinicians to evaluate individuals for a range of potential outcomes that are associated with, but not unique to, prenatal alcohol exposure. In addition, alternative diagnoses must be excluded and the potential influence of other adverse exposures assessed. Diagnostic criteria used internationally are based on criteria developed in North America. Research is required to ensure that diagnostic criteria and methods recommended for use in Australia are validated in the

Australian context, and can be updated to include new diagnostic technologies or diagnostic classifications when appropriate.

As reported in previous Telethon Kids Institute Annual Report Scientific supplements, a Final Report was submitted to the Commonwealth Department of Health in 2012. Five papers were published in 2012 – 2013 and a final paper published in 2014. Watkins RE, Elliott EJ, Wilkins A, Latimer J, Halliday J, Fitzpatrick JP, Mutch RC, O’Leary CM, Burns L, McKenzie A, Jones HM, Payne JM, D’Antoine H, Miers S, Russell E, Hayes L, Carter M, Bower C. Fetal alcohol spectrum disorder: development of consensus referral criteria for specialist diagnostic assessment in Australia. *BMC Pediatrics* 2014, 14:178

Funding: Commonwealth Department of Health and Ageing

FASD Diagnostic Instrument for Australia Trial and Implementation

Investigators: Carol Bower¹, Elizabeth Elliott², Rochelle Watkins¹

Project staff: Juanita Doorey¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

² Discipline of Paediatrics and Child Health, Sydney Medical School, University of Sydney, Sydney Australia

The Telethon Kids Institute, in collaboration with the University of Sydney, developed a diagnostic instrument for FASD for use in Australia,

on contract from the Commonwealth Department of Health and Ageing. Following its development, the Commonwealth Department of Health contracted the Telethon Kids Institute in 2014 to trial the implementation of the diagnostic instrument for FASD, again in collaboration with the University of Sydney.

The specific objectives of the project are to:

- Develop guidelines for health professionals on how to use the diagnostic instrument;
- Develop guidelines for support and referral pathways for families when a family member is diagnosed with FASD;
- Finalise the diagnostic instrument for release Australia-wide;
- Develop training resources for health professionals to support the national implementation; and,
- Establish a mechanism for the evaluation of the use of the diagnostic instrument.

An Expert Review Panel and project Steering Group have been established, recruitment of clinicians across Australia has commenced and ethics applications have been submitted.

Funding: Commonwealth Department of Health and Research Fellowship 634341

FASD in the juvenile justice system: a feasibility study of screening, diagnosis and workforce development

Investigators: Rochelle Watkins¹, Carol Bower¹, Raewyn Mutch¹, Rhonda Marriot², Steve Zubrick¹, Carmella Pestell³, James Fitzpatrick¹, Peter Collins⁴, Jonathan Carapetis¹

Project staff: Roslyn Giglia¹, Candice Rainsford¹, Jacinta Freeman¹, Natalie Kippin¹, Bernadette Safe¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

² Murdoch University, Perth, Australia

³ University of Western Australia, Perth, Australia

⁴ Aboriginal Legal Service, Perth, Australia

In 2013 the Alcohol and Pregnancy and FASD Research Group 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 aim of this research is 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.

2014 saw the bulk of the foundation work for the implementation of the research project at Banksia Hill Detention Centre (Banksia Hill DC). Most often referred to as the 'Banksia Hill' project, work has progressed to include:

- The conferment of ethics from the WAAHEC and UWA HREC.

- The establishment and meeting of a Steering Group, and a Community and Consumer Representative Group.
- The advertising for the employment of a research officer, speech pathologist and occupational therapist who will be based at Banksia Hill DC as part of the diagnostic assessment team.
- The advertising for two research positions (PhD or Postdoc) supported by the project to investigate; 1) a qualitative case study of the entire research process, and 2) a workforce development project to provide staff with support in managing young people (detainees) with FASD.
- The enrolment of a neuropsychologist (PhD/Masters student with supervision) as part of the diagnostic assessment team.
- The engagement of Banksia Hill DC staff in the research program and the establishment of a dedicated work space at the centre.
- The development of a final research protocol for the Department of Corrective Services which when approved will allow the research pilot to take place.

In bedding down the research protocol there were many challenges which needed to be overcome to ensure project rigor, acceptance, and clear research outcomes articulated to all key stakeholders. 2015 will see the

team move forward and build upon the strong foundation of collaboration and commitment that has been developed during 2014.

Funding: NHMRC Targeted Call for Research: Fetal Alcohol Spectrum Disorder among Aboriginal and Torres Strait Islander Peoples 1072072 and Research Fellowship 634341

Understanding FASD – a guide for justice professionals

Investigators: Heather Jones, Raewyn Mutch, Rochelle Watkins, Carol Bower

Telethon Kids Institute, The University of Western Australia, Perth, Australia

In 2011 and 2012 we conducted the 'Fetal Alcohol Spectrum Disorder: Knowledge, attitudes and practice within the Western Australian Justice System' project with the aim of assessing justice professionals' (judicial officers, lawyers, corrections staff, police officers) awareness and knowledge of FASD, the perceived impact of FASD on practice within the justice system, and to identify the information needs relating to FASD for the justice system in WA. When asked if they would like more information about FASD 93% of judicial officers responded positively.

Our research on FASD knowledge, attitudes and practice of justice professionals in WA identified:

- what information is required by justice professionals; and
- how this information should be delivered

GROUP NAME

The purpose of this project is to translate this research into educational resources for justice professionals so that they can:

- recognise cognitive impairments and possible FASD in young people engaging with the criminal justice system whether as a victim, witness or offender; or otherwise engaged in, or the subject of legal proceedings
- identify legal implications
- consider referral for assessment if the disability is suspected
- consider decision making with respect to orders, sentencing and management

In 2014 a Steering Group with representation from the courts, legal organisations and the community was formed to provide high level advice and expertise into the development of FASD educational resources for justice professionals:

- 5 short videos for judicial officer (judges and magistrates) and lawyers
- On-line CPD module for lawyers
- Information on FASD for the WA Bench Book which is used by all judges and magistrates in WA
- Presentations at conferences and seminars + training and education sessions
- FASD and Justice section on the Alcohol and Pregnancy and FASD website

Funding: Department of the Attorney General Criminal Confiscation of Property Grants Program

The Alert Program: An evidence based treatment program for Aboriginal children living with FASD

Investigators: James Fitzpatrick¹, Karen Edmond², Jane Latimer³, Branko Celler⁴, Trevor Mazzucchelli⁵ Glenn Pearson¹, Heather Carmichael Olsen⁶, Rochelle Watkins¹, John Boulton⁷, Maureen Carter⁸

Project staff: Bree Wagner¹, Kaashifah Bruce¹, Martyn Symons¹

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia

²Winthrop Professor of Aboriginal Clinical Child Health, The University of Western Australia, Perth, Australia

³The George Institute for Global Health, University of Sydney, Sydney, Australia

⁴Digital Productivity and Services Flagship, CSIRO, New South Wales, Australia

⁵Psychology and Speech Pathology, Curtin University, Perth, Australia

⁶Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, USA

⁷Professor of Paediatrics, Kimberley Paediatric and Child Health Team

⁸Nindilingarri Cultural Health Services, Fitzroy Crossing, Australia

Children with FASD and early life trauma can experience difficulties with

their self-regulation and executive functioning. This can impact on children's ability to plan, organise, maintain attention and choose an appropriate level of alertness to suit a particular task or situation. The Alert Program® is based on the analogy of the body being like a car engine to teach self-regulation and improve executive functioning. The body can run at different levels of alertness such as high, low or just right. Children are taught five ways to change their level of alertness through listening, moving, touching, looking or putting something in their mouth. The program also supports families, teachers and therapists to develop strategies to change or maintain states of alertness to optimise student functioning. Whilst initially designed for children with attention and learning disabilities, the program can be tailored to meet the needs of a specific population, such as children in the Fitzroy Valley, so that the concepts can be most effectively taught.

The goal of this research project is to develop, implement and evaluate the Alert Program® to improve self-regulation and executive functioning skills of primary school aged children in the Fitzroy Valley.

Alert Program® study objectives

- Establish a therapeutic program governance structure, representing community/families, schools, and child health services within the existing Marulu FASD Strategy Leadership Team.
- Identify children with impairments in self-regulation and executive functioning by screening and assessing school-aged children in the Fitzroy Valley, and accessing results of prior assessments (including those conducted during the Lililwan FASD prevalence study).
- Conduct consultation with community, schools, and child health services to tailor the Alert Program® and select measures of self-regulation and executive functioning to ensure cultural appropriateness and local relevance.
- Conduct training with teachers, Aboriginal school support staff and child health service providers in the delivery of the tailored Alert Program®.
- Determine the effectiveness of the tailored Alert Program® using a step wedged randomised controlled study design. This design introduces the Alert Program® to different schools at different times and compares outcomes for students before and after the program is implemented at each school. Quantitative data (numbers) will be collected to measure the effectiveness of the program at improving children's self-regulation and executive functioning. Qualitative (stories) data will determine provider/family satisfaction with the program.
- Provide parent/carer education and

training to increase their knowledge of how strategies utilised in the tailored Alert Program® can assist children to self-regulate

Funding: NHMRC Program Grant 1086145

Fetal Alcohol Spectrum Disorders (FASD) in the National Disability Insurance Scheme (NDIS)

Investigators: James Fitzpatrick, Tanyana Jackiewicz, Carol Bower

Project staff: Angela Dudley

Telethon Kids Institute, The University of Western Australia, Perth, Australia

In 2014 we received funding to conduct a comprehensive review of the available information, both published and unpublished on services and supports for people living with FASD to inform the development of draft best practice guidelines for NDIA planners. The work which will commence in 2015 will:

- develop a draft functional severity index for people with FASD to assist planners in decision making around the level and type of services and supports required
- estimate service cost estimates including workforce requirements for evidence based and promising services and supports
- present these draft guidelines and functional severity index for assessment by the NDIA Expert Panel

Funding: National Disability Insurance Agency

Staff and Students

Head of Alcohol & Pregnancy & FASD Research Group

Professor Carol Bower MBBS, MSc, PhD, FAFPHM, DLSHTM, FFPHA

Senior Principal Research Fellow, Telethon Kids Institute

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

Leadership Group

Dr James Fitzpatrick BSc (Physiology and Psychology), MBBS, PhD candidate

McCusker Clinical Research Fellow in Aboriginal Child Health, Telethon Kids Institute

Dr Rochelle Watkins BAppSc (Physiotherapy), PhD, Grad Dip Mgmt

Senior Research Fellow, Telethon Kids Institute

Dr Roslyn Giglia BAppSc (Nutr&FoodSci), Grad Dip Dietetics, MPH, PhD,

Senior Research Fellow, Telethon Kids Institute

Advanced Practicing Dietitian

Group Members

Kaashifah Bruce – Marulu FASD Prevention Strategy Coordinator

Juanita Doorey – Senior Research Officer

Heather Jones – Manager FASD

Projects

Associate Professor Raewyn Mutch –
Clinical Research Fellow

Candice Rainsford – Project Officer

Dr Tracy Reibel – Senior Research
Fellow

Gayle Segar – Patches Fitzroy Valley
Paediatric Clinic Coordinator

Dr Martyn Symons – Senior Research
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Assisted Reproductive Technology and Birth Defects

*Investigators: Dr Michele Hansen, Prof
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Assisted Reproductive Technologies (ART) are commonly used; 1 in 25 children in Australia are born as a result of ART treatment such as IVF and this figure rises to 1 in 7 for women over 37 years of age. Hence it is important to evaluate the safety of ART treatment by examining health outcomes in the children born. We have been studying health outcomes with a particular focus on birth defects since 2002 and

were invited to contribute to a 2014 special edition of Seminars in Fetal and Neonatal Medicine titled “IVF – Impact on Fetal and Neonatal Outcomes.” Our paper on intrauterine growth and birth defects summarised current evidence and the implications for future research in this field.

There have been substantial changes to IVF clinical practice in the last 10 years but little is known about child health outcomes following these shifts in treatment. Specifically, there are no reliable birth defects data available internationally subsequent to the use of recent techniques such as extended embryo culture (blastocyst transfer) and rapid embryo freezing (vitrification). This information is essential for appropriate pre-treatment counselling and to inform best practice in Australian ART clinics. Western Australia (WA) is the only State with a statutory Register of all ART treatment that exists alongside an extensive system of population-based health datasets. In 2014 we were successful in obtaining a 3-year NHMRC project grant to continue our work examining intrauterine growth and birth defects in a more recent cohort of ART births (2003-2013). Our project will link several WA datasets together with information from the national Pharmaceutical Benefits Scheme (PBS). This will allow us, for the first time, to identify not only naturally conceived children and those born following ART, but also those born outside the fertility clinic setting following



controlled ovarian hyperstimulation and intrauterine insemination or ovulation induction alone.

We also collaborated with Dr Georgina Chambers and colleagues at the National Perinatal Epidemiology and Statistics Unit to conduct an economic assessment of the frequency, duration and cost of hospital admissions during the first 5 years of life for singleton, twin and higher order multiple (HOM) children, and to examine the contribution of ART to the incidence and cost of multiple births. The study, published in JAMA Pediatrics, included all children born in Western Australia 1994-2003 with follow up to 2009 (226,624 singletons, 6941 twins and 285 higher order multiples (HOMs)). We found that 1.0% of singletons, 15.4% of twins and 34.7% of HOM children were conceived following ART. Compared with singletons, twins and HOMs were 3.4 and 9.6 times more likely to be stillborn, and 6.4 and 36.7 times more likely to die during the neonatal period. Twins and HOMs were 18.7 and 525.1 times more likely to be preterm, and to be small for gestational age. The average hospital cost of singleton, twin and HOM children to 5 years was \$2730, \$8993 and \$24,411 (USD 2009/10) respectively, with cost differences concentrated in the neonatal period and during the first year of life. Our results indicated that 15% of hospital costs for multiple births could have been avoided if ART twins and HOM were born as singletons. This paper was particularly aimed at a US audience where persistently high ART

multiple birth rates highlight the need for strategies that encourage single embryo transfer.

Funding: NHMRC Project Grant #211930; NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB). New funding obtained in 2014: NHMRC Project Grant #1086530; NHMRC Early Career Fellowship #1090648 (MH).

Autism Research Team

The Autism Team conducts cutting-edge research into the causes of autism, and discovering new ways to help people with autism live the most fulfilling life possible.

The two research aims of our team are:

- To identify the causes of Autism Spectrum Disorders(ASD) and related conditions; and
- To discover new and innovative ways to help individuals with ASD

Overall we wish to create a better future for individuals with ASD.

The Autism Research Team is continuing to conduct a range of significant and diverse studies including Randomized Controlled Trials (RCT's)...

In 2014, we started a national project in collaboration with the Autism Cooperative Research Centre (www.autismcrc.org.au) to create an Australian Autism Biobank. A 'biobank' is simply a storehouse of biological information, such as blood and DNA. It is now widely thought that ASD is not one condition

with one cause, but many different conditions with many different causes. This means that to identify all of the different causes of ASD (and there are likely dozens of these, if not hundreds!), we need to study the genetics of as many individuals with ASD

and their families as possible. Australia has never had such a resource, and so we've decided to create one! Many families will have participated in our team's Western Australian Autism Biological Registry (WAABR), which has been an enormous success. Now, with funding from the Autism Cooperative Research Centre, we are collecting this same information from families in three other states: Victoria, New South Wales and Queensland. This national project is led by our research team, and we believe that it will bring about a revolution in Australian research into the causes of ASD. You can see an article about this exciting project here:

<http://goo.gl/kmxo2x>

Clinical Trials

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:

- 1) To determine the effectiveness of TOBY Playpad as a complement

to any community therapy a child is receiving, and

- 2) 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.

Recruitment for this project finished on the 31st of October, 2014. TOBY families will be followed for the next 6 months with data analysis and preliminary results to follow in late 2015.

Funder of the project: Australian Children's Trust

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.

This trial will finish recruitment in early 2015.

Funder of the project: NHMRC

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.

Funder of the project: NHMRC

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.

Autism and 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.

Funder of the project: NHMRC

Other Autism related research we've been conducting includes:

- Brain processing of pictures and words
- Dental Health
- Lung Function
- Face Structure
- Prenatal Brain Development

The natural history of the CDKL5 disorder: development of an international register

Investigators: 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 253 families had been recruited and over 80% had provided data. In June 2014 we presented findings to families and clinicians at the 2nd International CDKL5 Research Symposium and Family Conference in Washington DC. We presented information on the functional abilities of individuals with the CDKL5 disorder, the occurrence and impact of gastrointestinal problems and

the treatment and pattern of epilepsy. Stephanie Fehr submitted her PhD on the database and its outcomes to date in November 2014.

Funders of the project: International CDKL5 Foundation, NHMRC Program Grant (572742), NHMRC Senior Research Fellowship Helen Leonard (572568), Australian Postgraduate Award, University of Western Australia Safety-Net Top-Up Scholarship, the Stan and Jean Perron Top-Up Scholarship and the Stan and Jean Perron Award for Excellence (Stephanie Fehr).

Childhood Cancer Epidemiology

Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children

Investigators: 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 following papers using data from this study were published in 2014:

Evans T-J, Milne E, Anderson D, de Klerk NH, Jamieson SE, et al. Confirmation of Childhood Acute Lymphoblastic Leukemia Variants, ARID5B and IKZF1, and Interaction with Parental Environmental Exposures. *PLoS ONE* 2014; 9(10): e110255 doi:10.1371/journal.pone.0110255

Bailey HD, Miller M, Greenop KR, Bower C, Attia J, Marshall G, Armstrong BK, Milne E. Paternal intake of folate and vitamins B6 and B12 before conception and risk of childhood acute lymphoblastic leukemia. *Cancer, Causes and Control* 2014 Dec;25(12):1615-25.

Bailey HD, Fritschi L, Metayer C, Infante-Rivard C, Magnani C, Petridou E, Roman E, Spector LG, Kaatsch P, Clavel J, Milne E, et al. Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. *Cancer Causes and Control* 2014; 25:1351-1367

Metayer C, Milne E et al. Maternal Supplementation with Folic Acid and Other Vitamins and Risk of Leukemia in the Offspring: a Childhood Leukemia International Consortium Study *Epidemiology* 2014. 25:811-822.

Bailey HD, Fritschi L, Infante-Rivard C, Glass DC, Miligi L, Dockerty JD, Lightfoot T, Clavel J, Roman E, Spector LG, Kaatsch P, Metayer C, Magnani C, Milne E, Polychronopoulou S, Simpson J, Rudant J, Sidi V, Rondelli R, Orsi L, Kang A, Petridou E, Schüz J. Parental

occupational pesticide exposure and the risk of childhood leukemia in the offspring: Findings from the Childhood Leukemia International Consortium. *International Journal of Cancer* 2014 135, 9, 2157-72.

Peters S, Glass DC, Milne E, Fritschi L. Rule-based exposure assessment versus case-by-case expert assessment using the same information in a community-based study. *Occupational and Environmental Medicine*. 2014;71: 215–219.

Funders of the project: NHMRC Grant #254539, and Cancer Council WA.

National Case-Control Study of the Causes of Childhood Brain Tumours

Investigators: 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 2014:

Greenop KR, Miller M, Attia J, Ashton LJ, Cohn R, Armstrong BK, Milne E. Maternal consumption of coffee and tea during pregnancy and risk of childhood brain tumors: Results from an Australian

case-control study. *Cancer Causes and Control*, 2014; 25, 1321-1327.

Greenop KR, Miller M, de Klerk NH, Scott RJ, Attia J, Ashton LJ, Dalla-Pozza L, Bower C, Armstrong BK, Milne E. Maternal dietary intake of folate, and vitamins B6 and B12 during pregnancy and risk of childhood brain tumors. *Nutrition and Cancer: An International Journal* 2014: 66, 800-809.

Peters S, Glass DC, Greenop, KR, Armstrong, BK, Kirby M, Milne E, Fritschi L. Childhood brain tumors: Associations with parental occupational exposure to solvents *British Journal of Cancer*. 2014; 111(5) p 998-1003

Greenop KR, Hinwood A, Fritschi L, Scott RJ, Attia J, Ashton LJ, Heath J, Armstrong BK, Milne E. Vehicle refuelling, use of domestic wood heaters and the risk of childhood brain tumors: results from an Australian case-control study. *Pediatric Blood & Cancer* (online 4 Oct 2014) DOI: 10.1002/pbc.25268.

Milne E, Greenop KR, Fritschi L, Attia J, Bailey H D, Scott RJ, Ashton LJ, Smibert E, Armstrong BK Childhood and Parental Diagnostic Radiological Procedures and risk of Childhood Brain Tumors. *Cancer Causes and Control*. 2014;25:375–383.

Greenop KG, Peters S, Fritschi L, Glass DC, Ashton LJ, Bailey HD, Scott RJ, Daubenton J, de Klerk NH, Armstrong BK, Milne E. Exposure to household painting and floor treatments, and parental occupational painting and the risk of childhood brain tumors:

results from an Australian case-control study. *Cancer Causes and Control*. 2014;25:283–291.

Greenop K, Blair EM, Bower C, Armstrong BK, Milne E. Factors relating to pregnancy and birth and the risk of childhood brain tumors: Results from an Australian case-control study. *Paediatric Blood and Cancer*. 2014;61:493–498.

Funders of the project: NHMRC Grant #404089.

Nutrition and Genome Health in Children

Investigators: 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. The following papers were published in 2014:

Ramankutty P, Klerk NH, Miller M, Fenech M, O'Callaghan N, Armstrong BK, Milne E. Ultra-violet radiation exposure and serum vitamin D levels in young children. *Journal of Pediatric and Child Health* 2014. 50, 9 713-720.

Funders of the project: NHMRC Grant#572623.

Childhood Cancer Epidemiology: other work

Sadetzki S, Langer CE, Bruchim R, Kundi M, Merletti F, Vermeulen R,

Kromhout H, Lee AK, Maslanyj M, Sim M, Taki M, Wiart J, Armstrong BK, Milne E, et al. The MOBI-Kids study protocol: Challenges in assessing childhood and adolescent exposure to electromagnetic fields from wireless telecommunication technologies and possible association with brain tumour risk. *Frontiers in Public Health* 2014; 2:124.

Collaboration for Applied Research and Evaluation

The Collaboration was established by the Telethon Kids 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.

In line with the mission of Telethon Kids, the focus of the Collaboration is to contribute to the health and wellbeing of Western Australian children and their families. This role in seeking to promote health and wellbeing and to reduce the burden of illness among children clearly aligns with the goals of the State's public health system.

The Strategy of the Collaboration

Research driven by the priorities of the WA Department of Health, other government agencies, non-government agencies and industry is the focus of the Collaboration.

The mission of the Collaboration is utilize our unique research expertise

and capabilities 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.

The strategic approach of the Collaboration in relation to securing research funding over the next 3 to 5 years includes the following:

1. To tender successfully for quality improvement, research, and evaluation work on the behalf of agencies such Department of Health and Department of Education and commonwealth equivalents.
2. To diversify the financial reach of the Collaboration by responding to opportunities from the Department of Child Protection and Family Support; Department of Education; Disability Services, Department of Justice, the Commissioner for Children and Young People and Commonwealth Agencies as well as the non-government sector.
3. To actively investigate other means of research funding based on the priorities of the Institute and the expertise of the team.

The Collaboration's strategic approach over the next 3-5 years will be achieved through a program of work that focuses, through the Collaboration, the Institute's skills on:

1. Local priorities of government and non government agencies.
2. Our unique ability to function as a “research framing consultancy”
3. Partnerships with government agencies, non government agencies and other stakeholders that facilitate the setting of priorities in child and youth health and wellbeing.
4. Our research expertise and capabilities (“technologies”) including:
 - a. Qualitative research
 - b. Conduct of comprehensive research programs involving a number of research modalities
 - c. Program and Project Evaluation
 - d. Program/Intervention Development
5. Translating research evidence into practical strategies and interventions (design and evaluation) to reduce avoidable cost burdens on the health system.
6. Profiling evidence based service delivery to assist health organisations in ensuring their services are cost effective and of the highest quality.
7. Evaluating program and service studies that offer guidance in optimising delivery in different settings and for different populations.
8. Analysing data to identify trends in areas of interest to our stakeholders.
9. Identifying cost effective

preventive measures that will assist agencies to achieve its resource management goals.

10. Working collaboratively with other internal Telethon Kids research groups (such as the Human Capabilities Team)

11. Supporting translation across all research at the Institute including offering strategic support to the Knowledge Translation Manager.

Program of Research

The Collaboration’s program of work currently spans four domain areas:

- Services for Healthy Children
- Services for Healthy Early Years
- Services for Healthy Adolescents
- Services for Healthy Pregnancy and Birth

The following provides a summary of research projects completed in the calendar year 2014; as well as ongoing research projects.

Completed research (2014)

Services for Healthy Early Years

A Pathway from Early Childhood Disadvantage

Investigators: Dr Kim Clark and Tanyana Jackiewicz (Telethon Kids)

Why was this research conducted?

This project was initiated by the Minderoo Foundation and entailed

detailed review of the Challis model (located in Armadale, WA) and the evidence supporting it with the view to advocating its relevance for implementation in other vulnerable areas of Australia. This project follows extensive work and collaboration in both developing and implementing the Challis model by a range of government and non-government agencies and groups over more than 5 years. In carrying out the project, the Institute reviewed documentation on the Challis community model, critically analysed relevant academic literature, and examined trend data from the community.

How has the research been used?

The rapid and significant signs of the Challis model's success in altering the life course of local children have encouraged stakeholders, including the Minderoo Foundation, to seek to share the findings and to suggest the policy relevance of the Challis model as a low-cost, evidence supported Australian strategy for reducing long-term disadvantage and its associated social and economic costs. They did this by launching the report at the October 2014.

Synopsis

The paper attempts to situate itself as reflecting a next generation of knowledge about ways in which Australian governments can effectively reduce entrenched disadvantage across the Nation, bringing together evidence from a spectrum of disciplines spanning brain science, organisational

leadership, early childhood education, and service integration.

Funders of the project: Minderoo Foundation

Services for Healthy Pregnancy and Birth

Evaluation: Alcohol in Pregnancy Campaign

Investigators: Dr Tracy Reibel and Tanyana Jackiewicz (Telethon Kids), Drug and Alcohol Office (DAO)

Why was this research conducted?

Strong Spirit Strong Future (SSSF) is the state-wide Aboriginal fetal alcohol spectrum disorder (FASD) Prevention Program, coordinated by the Drug and Alcohol Office (DAO). The DAO sought an independent evaluation of the SSSF Project to ensure they had implemented the SSSF according to best practice. Further, they wanted to use the results of the evaluation to inform future prevention programs in the alcohol and other drugs area for Aboriginal people.

How has the research been used?

This retrospective 'process' evaluation utilising a purpose built evaluation tool has provided independent evidence that the SSSF Program has incorporated all the elements in the literature suggesting effectiveness in reducing alcohol consumption in pregnancy. The DAO have indicated that they will be using the Telethon Kids report to request additional funding to support the program's activities in the coming years. The evaluation will also be used



as a pre-cursor to an impact evaluation to determine whether the SSSF has resulted in behavioural changes among the target group. Finally, an output of the evaluation included a set of best practice indicators that has redefined health promotion programs for Aboriginal audiences. This combined with the complete documentation of the SSSF Program from inception to implementation means the SSSF Program can be replicated elsewhere.

Synopsis

The SSSF Project comprised three components: [1] a mass reach media campaign; [2] community resources promoting the NHMRC guidelines regarding alcohol use in pregnancy; and, [3] workforce development. The process evaluation sought to determine whether SSSF met its stated aims and objectives, and whether it was implemented in accordance with a framework of evidence-based and culturally informed consultation and development. Having considered all the evidence, the evaluators were able to confidently state that DAO through the SSSF has achieved a robust, acceptable and appropriate health promotion campaign. The Project meets the criteria for best practice in Aboriginal health promotion practice and is an exemplar of process, from conception and design through to application. Drawing on the evaluation outcomes and building on the purpose specific evaluation tool, a set of best practice principles in Aboriginal alcohol and other drugs health promotion programs

was developed as part of the research outputs.

Funders of the project: WA Department of Health

Informing Pregnancy Care for Young Aboriginal Women

Investigators: Dr Tracy Reibel, Lisa Morrison (Telethon Kids), Aboriginal Maternity Services Support Unit, Women and Newborn Health Service

Why was this research conducted?

This project was conducted as part of the Aboriginal Maternity Services Support 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 had not previously been conducted on a wide scale in a range of locations in Western Australia to explore what their views of antenatal care services are. This project aimed to inform the delivery of culturally and age appropriate services that improve access to and sustained use of antenatal services by adolescent Aboriginal women (<20 years).

How has the research been used?

This research has informed the continuing work of the AMSSU towards improving service and health provider knowledge of Aboriginal perspectives of maternity care. The recommendations have been combined with another report as the basis of a service provider workshop to identify

which of the recommendations can be implemented within existing service frameworks and resources. The final project report was also submitted to the State Parliamentary Enquiry into the Patient Assisted Transport Scheme. A journal article has been submitted and accepted for publication.

Synopsis

The main research question was: What are the essential elements of antenatal services that encourage young (<20 years) pregnant Aboriginal women to access antenatal care early in pregnancy as well as continue to access this care. This project was undertaken to improve understanding of young Aboriginal women's knowledge of pregnancy and identify factors that may encourage them to seek early pregnancy care. The study sample was recruited from metropolitan, regional and remote parts of Western Australia including those in the main target group (pregnant Aboriginal women or birth mothers 16-21 years); elder women and other Aboriginal community members; and, health and other professionals working in relevant settings. The primary area of concern noted in the study relates to young Aboriginal women living in locations without birth services and being required to leave their home communities to attend another location for childbirth up to six weeks prior to their due date. Young women require familial support during a vulnerable time in their lives. A documented patient relocation pathway for those required

to leave their home communities would improve the cultural security of antenatal service delivery.

Funders of the project: WA Department of Health

Improving Journey Planning for Pregnant Aboriginal Women

Investigators: Dr Paula Wyndow, Tanyana Jackiewicz (Telethon Kids), Aboriginal Maternity Services Support Unit, Women and Newborn Health Service

Why was this research done?

Despite making substantial improvements in the health of Aboriginal Australians over the last ten years, significant gaps between Aboriginal and non-Aboriginal people in maternal and infant health outcomes remain. This project responded to concerns regarding Aboriginal women, and their babies, and the impact of the lack of documented patient transfer models for journey planning (through antenatal, birth, postnatal, and primary care). The Aboriginal Maternity Services Support Unit (AMSSU) engaged with the Telethon Kids Institute to undertake research with the view to improving the patient journey for pregnant Aboriginal women and their families.

How has the research been used?

This report has been submitted to the Parliamentary Inquiry into the Patient Assisted Transport Scheme (PATS) currently taking place in Western Australia and is currently being used as a basis for planning for the priorities and

GROUP NAME

focus of the work of the AMSSU.

Synopsis

The overall aim of this project was to determine the feasibility of an integrated model of care for Aboriginal women in Western Australia during pregnancy. To do this it was important to understand the current system of identification, referral, and support available and to identify barriers that prevent important information related to these women and their babies being transferred between these services.

This research, with the support and involvement of appropriate governance structures involved the conduct of focus groups and one on one interviews across Western Australia. Overall, health professionals agreed that the development of an integrated journey plan needed to occur at the level of the health region, rather than State-wide. There was an optimism that each region, supported by an inclusive consultation process could develop their own pathway model of care that would help facilitate a culturally secure supported journey for Aboriginal women and their families throughout the pregnancy journey and beyond. The consultation did however, identify significant political, organisational, structural and cultural barriers to developing these journey plans. Overcoming these barriers was not considered to be insurmountable as the consultation revealed that there was a need to adopt a region-specific collaborative approach to investing in maternal and child health services

for the long term. This is seen as successfully engendering respectful and trusting relationships between service providers and the Aboriginal people they support.

Funders of the project: WA Department of Health

Services for Healthy Adolescents

A 15 year Follow-up of Children of Participants in a Parenting Intervention

Investigators: Grant Smith (Telethon Kids), Child Adolescent Community Health, Child Adolescent Health Service

Why was this research done?

The Triple P Positive Parenting Program is a behavioural family intervention that aims to promote optimal child development and prevention of childhood behavioural disorders through enhancing 'positive parenting practices'. Despite a substantial amount of research evidence being available on the short term outcomes associated with this Program, high quality long-term research into the effectiveness of Triple P is sparse. Given the widespread use of Triple P, particularly in Western Australia, the need for evidence examining the long-term effects is required.

How has the research been used?

This research provides promising evidence of a long term effect of Triple P in regard to educational achievement as well as emergency department presentations that can be used to

inform future support of the Triple P program in Western Australia.

Synopsis

This study followed up a cohort of children whose parents took part in a quasi-experimental trial of Triple P conducted by Telethon Kids in 1996. Up to 15 years' worth of administrative records from Western Australian Departments of Education, Health, and Corrective Services were linked to the trial records to determine whether the intervention was associated with long-term differences in: emergency department (ED) admissions, hospitalisations, community mental health contacts, academic achievement, school attendance, teenage births, and court appearances. Triple P was associated with a 15.9% reduction in the rate of ED admissions across childhood/adolescence. Further, the pattern of results strongly suggest that the Triple P resulted in a lasting, long-term positive effect on literacy and numeracy achievement. Evidence of the impact of the Triple P was observed when examining outcomes measured over primary school (reading and numeracy) and upper secondary school (school attendance). Given the relatively minimal time burden posed by the intervention, the magnitudes of the observed effects are not insubstantial; based on the results Triple P appears to provide a minimal-investment solution for parents to provide a meaningful long-term benefit to their child's developmental trajectory. The fact that this eight-week group-based

behavioural parenting intervention was associated with higher reading achievement over the ages of seven to 12 years, consistently higher numeracy achievement up to the age of 12 years, and 22.9% fewer days absent from upper secondary school is, whilst not unexpected, very encouraging. Furthermore if future research indicates a causal role of Triple P in reducing ED visits, a 15.9% fewer ED admissions between the ages of eight and 20 years also represents a significant impact. Where the picture is less clear, however, is with regard to the effect of Triple P on utilisation of community mental health services.

Ongoing Research (2014)

Services for Healthy Children

Child Development Information System Project

Investigators: Grant Smith (Telethon Kids), John Wray (Child Development Service, Child Adolescent Community Health)

The aim of this project is to provide analytical support to the Child Development Service (CDS) by analyzing the Child Development Information System (CDIS) according to policy-relevant research questions of interest to the CDS. CDIS contains information on all clients of Child Development Services across the metropolitan area. CDIS is used by pediatricians and allied health professionals in the CDS to manage

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cases. Clinically relevant information is entered in the database; allowing quick retrieval for future visits and effective sharing of information across CDS professionals. This system has an impressive number of records (over 20,000 clients with over 100,000 occasions of service) with a wide range of clinical information stored within the database; making it a potentially invaluable tool for research. The system has been running for approximately four years. However, universal uptake of the system occurred approximately two years ago: this allows analysis of the previous two years of collected clinical information.

This research partnership has allowed a Telethon Kids researcher to be co-located with the CDIS Team to allow for greater degree of collaboration and working relationships to be developed with the view of producing more relevant outcomes from the analyses.

Funders of the Project: WA Department of Health

Anaemia in Western Australia: incidence in Aboriginal and non-Aboriginal populations across the state

Investigators: Grant Smith (Telethon Kids), Professor Karen Edmond (Princess Margaret Hospital)

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 middle of 2015.

Funders of the project: WA Department of Health

Services for Healthy Early Years

Evaluation of the integrated service initiatives targeting the early years in Western Australia

Investigators: Dr Kim Clark, Rhonda Breen (Telethon Kids), Sue Kiely (Child Adolescent Community Health, Child Adolescent Health Service)

This project explores 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 beginning of 2015.

Funders of the project: WA Department of Health

Services for Healthy Adolescents

Evaluation of the choice and partnership approach (CAPA) within Child and Adolescent Mental Health Services

Investigators: Dr Kim Clark, Tess Fletcher and Dr Rachel Skoss (Telethon Kids)

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 end of 2015.

Funders of the project: WA Department of Health

Western Australian Coronial Suicide Information System

Investigators: Tanyana Jackiewicz (Telethon Kids), Kirsten James, Michael Moltoni (Mental Health Commission), Gary Cooper (State Coroner's Office)

This project builds on more than 20 years' experience by Telethon Kids collecting and analysing information on suicides in Western Australia. With previous approval by the State Coroner, Telethon Kids has already collected comprehensive information on all suicides between 1986 and 2008. The new information system will include all this information as well as more recent information (contingent on formal approval from the Coroner) including information on suspected suicides to produce the most comprehensive information system on suicide in Australia. The Western Australian Coronial Suicide Information System is anticipated to:

- Provide easily accessible information on circumstances surrounding persons who die by suicide that will inform strategies to prevent suicide.
- Enable early detection of systematic trends such as hotspots and clusters to enable a comprehensive response aimed to prevent further suicides.
- Provide researchers with a database to investigate, among other things, relationships between risk factors to better understand the circumstances surrounding suicide in Western Australia to inform suicide prevention efforts.

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Funders of the project: Mental Health Commission until 2017.

Services for Healthy Pregnancy and Birth

A study examining post natal follow-up of women receiving pregnancy care with the Women and Newborn Drug and Alcohol Service (WANDAS)

Investigators: Anna Fletcher (Telethon Kids), Angela O'Connor (WANDAS), Renate McLaurin (WANDAS)

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 is currently underway with more than half of the case note review completed; brief interviews are in the field and in-depth interviews are being conducted where appropriate. A GP survey has been conducted. An interim report has been prepared. This project is due to be completed early 2015.

Funders of the project: WA Department

of Health

Western Australian Health and Pregnancy Surveillance System: Development of a statewide surveillance system

Investigators: Dr Paula Wyndow, Tanyana Jackiewicz (Telethon Kids), Professor Carol Bower (KEMH)

This project attempts to establish a state-wide capacity for the monitoring and surveillance of behavioural and other risk factors in pregnancy that lead to adverse outcomes such as birth defects. It requires the design and establishment of a database to store the data; as well as provide a data collection interface for participants to use when filling in their online questionnaires. The research infrastructure will be designed to ensure as far as possible the cost effectiveness of collecting the information on a long term basis. This project is due to be completed in 2016.

Funders of the project: WA Department of Health

Trial of a Novel Pregnancy Care Model for Women with Obesity

Investigators: Anna Fletcher, Lisa Gibson, Tanyana Jackiewicz (Telethon Kids), Professor Yvonne Hauck (KEMH)

This project builds on a previous research project that was conducted by Telethon Kids Institute. The outcome of that research project was an evidence-based, acceptable model of care designed to support women with

obesity to achieve a healthy gestational weight gain and reduce obstetric and neonatal complications called 'Blooming Together'. Blooming Together provides, among other things, early intervention (at 12-14 weeks gestation); comprehensive, clear, consistent and supportive lifestyle education and antenatal care; continuity of care (and peers) providing accountability for patients; as well as social support.

This new research looks at piloting the Blooming Together Program in its entirety to determine whether the Program can be delivered effectively in both a community and tertiary setting and to quantify the Program costs in the context of operational efficiency and Activity-based Funding. The first pilot commenced in December 2014 at the Woodbridge Women's Clinic, Rockingham. The second pilot will be at Fiona Stanley Hospital and will commence in April 2015. This project is expected to be completed in 2016.

Funders of the project: WA Department of Health

Maternal Satisfaction with Public Maternity Services in WA – Follow-on project

Investigators: Dr Kim Clark, Dr Tracy Reibel (Telethon Kids), Linda Sinclair (SOSU)

This research follows on from a previously funded project undertaken with the Department of Health's Statewide Obstetric Support Unit (SOSU) to develop and pilot a survey tool for use in monitoring women's

perspectives of public maternity services in WA. The requirement for this follow-on project was signalled in the initial proposal (Maternal Satisfaction with Public Maternity Services in WA) which pointed to further work being required to establish a model for field work in assessing women's satisfaction with public maternity services in each of the State's health regions.

The goals of the new research are to:

- Develop a step-by-step site guide for undertaking and using the results of maternity care experience surveys for WA maternity care providers;
- Provide a standard approach and a valid tool for evaluating mothers perspectives of public maternity care services in WA;
- Develop SOSU's capacity to evaluate Statewide implementation of the National Maternity Services Plan.

Funders of the project: Jointly funded by SOSU; Nursing and Midwifery Office and Research and Development at DOH

Publications and Reports

Kim Clark and Tanyana Jackiewicz
A Pathway from Early Childhood Disadvantage for Australian Children. Telethon Kids Institute, The University of Western Australia, under contract with Minderoo Foundation, October 2014

Paula Wyndow and Tanyana Jackiewicz

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Health Providers' perspectives on journey planning for pregnant Aboriginal women: A feasibility study. Telethon Kids Institute, The University of Western Australia under contract with the Department of Health, Western Australia; 2014

Tracy Reibel and Tanyana Jackiewicz Strong Spirit Strong Future Health Promotion Program: Process Evaluation Telethon Kids Institute, The University of Western Australia under contract with the Department of Health, Western Australia; 2014

Grant Smith 15 Year follow-up of WA Positive Parenting Trial, Telethon Kids Institute, The University of Western Australia under contract with the Department of Health, Western Australia; 2014

Reibel, T and Morrison L. Young Aboriginal Women's Voices on Pregnancy Care. Telethon Kids Institute, The University of Western Australia under contract with the Department of Health, Western Australia; 2014

Reibel T, Morrison L, Griffin D, Chapman L, Woods H Young Aboriginal Women's Voices on Pregnancy Care: factors encouraging antenatal engagement Women and Birth, 2014 28 (1): 47-53

Clark, K., Beatty, S., & Reibel, T. (2015). 'What Women Want': Using Image Theory to develop an expectations of Maternity Care Framework. Midwifery. In Press

Clark, K., Beatty, S., & Reibel, T. (2015). Maternity care: A narrative overview of what women expect across their care

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Oddy, W, Smith, G, Jacoby, P. (2014) A possible strategy for developing a model to account for attrition bias in a longitudinal cohort to investigate associations between exclusive breastfeeding and overweight and obesity at 20 years. Annals of Nutrition and Metabolism. 65(3): 234-235

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Disability

Down Syndrome Clinical Trial- BTD-001

Investigators and Associated Personnel: Helen Leonard, Jenny Downs, Jenny Bourke, Peter Richmond, Jasminka Murdzoska, Kingsley Wong, Tanya Stoney, Gabi Willis, Camille Gibson, Eloise Wilson, Kirsten Stirling, Barbara Anderson, Ushma Wadia

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. By year end 2014, 22 individuals had been screened and 14 had completed full participation. Further screening was anticipated into 2015.

Determinants and Outcomes of Preterm Birth & Pathways into Developmental Disorders

Investigators: Fiona Stanley, Helen Leonard, Claudia Slimings, Kristjana Einarsdottir, Jenny Bourke, Nick De Klerk, Peter Jacoby, Steve Ball, Gavin Pereira, Ravisha Srinivasjois, David Burgner, Jessica Miller, Emma Glasson, Jenny Fairthorne

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.

Current work published in 2014 included investigation of the relationship between various environmental factors and pregnancy complications and birth outcomes. Also published, and in the British Medical Journal, was an innovative

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study investigating the effect of inter-pregnancy on adverse birth outcomes such as pre-term birth, low birthweight and intrauterine growth retardation. Using novel methodology this study questioned some previous research findings on this topic. Further to these studies of the determinants of adverse birth outcomes we have started to investigate the later hospitalisation experience of children born at different gestational ages. Some of this work was published in 2014 while further studies are ongoing.

Another sequel to our examination of the causes of pre-term birth, 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.

Funders of the project: NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

Publications 2014

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Slimings, C., Einarsdóttir, K., Srinivasjois,

R. and Leonard, H. (2014), Hospital Admissions and Gestational Age at Birth: 18 Years of Follow Up in Western Australia. Paediatric and Perinatal Epidemiology, 28: 536–544. doi: 10.1111/ppe.12155

Pereira G, Bell M, Belanger K, de Klerk N. Fine particulate matter and risk of preterm birth and pre-labor rupture of membranes in Perth, Western Australia 1997–2007: A longitudinal study. Environment International. 2014; 73: 143-149

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Multi-Registry Analyses of Risk Factors for Autism: iCARE and MINERvA

Investigators: Diana Schendel, Michaeline Bresnahan, Kim Carter, Jakob Christensen, Lyn Colvin, Richard Francis, Mika Gissler, Emma Glasson, Nan Hu, Kingsley Wong, Therese Grønberg, Raz Gross, Nina Gunnes, Mady Hornig, Christina Hultman, Marlene Lauritsen, Helen Leonard, Erik Parner, Abraham Reichenberg, Sven Sandin, Andre Sourander, Camilla Stoltenberg, Auli Suominen, Pal Sureñ, 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

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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.

The work undertaken in 2014 has mainly involved the completion of ethics applications and applications for provision of the population data required at the seven sites in Scandinavia (Norway, Sweden, Denmark and Finland), Israel, the US (California) and Western Australia in the expectation of data delivery early 2015. Much time has been spent in the form of weekly teleconferences developing a manual for the harmonization processes which will need to occur at each site once the data is received. This has been developed in conjunction with the data analysts and those who are going to lead the individual projects which will occur. This large multinational research team looks forward with anticipation to the arrival of data in 2015 after which the harmonization work will commence to ensure the compatibility of all the local datasets.

Funders of the project: Autism Speaks (iCARE 6249), National Institute of Health (MINERvA (RFA HD-12-196)).

WA Cerebral Palsy Studies

Investigators: 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.

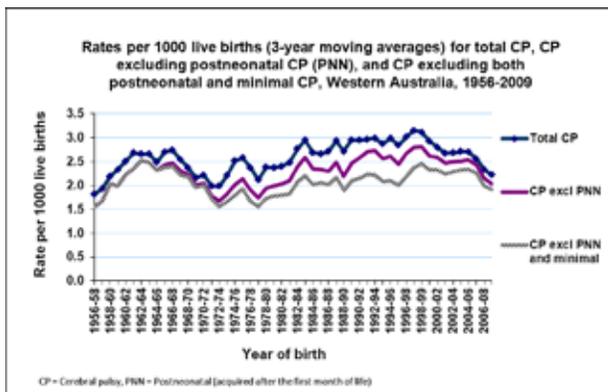
The WA Register of Developmental Anomalies - Cerebral Palsy

Investigators: 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 2009.

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 to the



CP Alliance Research Institute in NSW in 2007 by which time CP registers had been established in all States and Territories. The ACPR continues to flourish: The first report of the ACPR was published in 2009, and the second published in 2013 considers birth years 1993-2006. Both are available at <http://cpregister.com>. The most notable feature of the latest statistics, both from WA (see Figure) and the ACPR report, is the continued decline in proportion of live births subsequently meeting the criteria for CP, due primarily to the decrease in the proportion seen in very preterm births.

The WA investigators have contributed a number of papers to an ACPR supplement of the *Developmental Medicine and Child Neurology* journal aimed at show-casing the research supported by CP registers across Australia. Contributions to this supplement are now with reviewers.

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). The ACPR is supported by the CP Alliance (NSW) who are also funding the DMCN supplement.

Developing a reliable system of describing CP

Investigators: 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 Training and Reference dvd demonstrating how to use the CP Description form and the ASAS that includes examples of the different forms of CP is published and a limited number are available from Noula Gibson <Noula.Gibson@health.wa.gov.au>.

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

Investigators: Eve Blair, Sarah McIntyre, Linda Watson, Nadia Badawi, Karin Nelson

Comprehensive maternal, pregnancy, birth and neonatal information on all CP cases not postneonatically acquired, matched controls, and a representative sample of 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 at least 35 completed weeks of gestation (term and late preterm singletons). This relatively low risk group has received little research attention,

yet it contributes 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 term and late preterm singleton sample were considered neurologically normal 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 a career development grant from the CP Alliance provides additional funds for travel for EB.

Publications 2014

Hayley Smithers-Sheedy (authors listed

alphabetically)Nadia Badawi, Eve Blair , Christine Cans, Kate Himmelmann, Ingeborg Krägeloh-Mann , Sarah McIntyre, Jennie Slee, Peter Uldall, Linda Watson and Meredith Wilson. What constitutes cerebral palsy – in the twenty-first century? doi: 10.1111/dmcn.12262. *Developmental Medicine and Child Neurology*, 2014. 56(4):323-8.

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encephalopathy influence the outcome of treatment? *Developmental Medicine & Child Neurology*, in press.

Smithers-Sheedy, H., Raynes-Greenow, C., Badawi, N., McIntyre, S., Jones, C. on behalf of the Australian Cerebral Palsy Register Group (2014). Congenital cytomegalovirus is associated with severe forms of cerebral palsy and female gender in an Australian population cohort study. *Developmental Medicine & Child Neurology*, In press

Developmental Pathways to healthy child development and wellbeing

The Developmental Pathways in WA Children Project (DPP) links de-identified population level data from Western Australian government departments and agencies to investigate risk and protective factors leading to differences in developmental outcomes for children and youth. This project provides new knowledge to inform and enable future policy and prevention strategies to improve child health and wellbeing.

The DPP has taken a multidisciplinary and holistic approach to research into the health, development and wellbeing of children and youth, by initiating and utilising linked, longitudinal population level data. The data are used to determine risk and protective factors leading to poor and good outcomes in WA children. The DPP pioneered population level data linkage across multiple government service sectors

in Western Australia, creating a unique data resource for use by researchers and policy makers.

In collaboration with community and consumer groups and the State government agencies, the findings from the DPP aim to inform whole of government intervention and prevention strategies to improve outcomes, influence policy frameworks as well as evaluate and monitor existing initiatives and policies that affect the health and wellbeing of children, youth and their families.

The primary aims of this collaboration are to:

1. Extend and expand the pioneering population level data linkage across multiple disciplines and government sectors in Western Australia;
2. Ascertain whether changes in factors at the child, family and community level increase or reduce vulnerability to adverse outcomes in mental and physical health, education, child maltreatment, juvenile offending, in all Western Australian children;
3. Identify areas of prevention and intervention across multiple government sectors, particularly in regard to mental health, disabilities, child protection, juvenile justice, educational achievement and school attendance;
4. Use these data to evaluate existing government initiatives and determine, at a population level, how initiatives have impacted on educational, social and health outcomes;

5. Improve the collection, utilisation and reliability of Government department data in program evaluation and policy development; and

6. Respond to the government departments' agendas and policy frameworks, while enhancing whole of government initiatives.

This project is internationally innovative in its use of linked statutory and government agency data sets to measure and monitor child development and wellbeing at the population level. We are one of the few places in the world that has the depth and breadth of information, expertise and capacity not only to conduct cutting edge research, but also to translate the findings into policy and practice, thus making this project innovative on an international scale.

The project encompasses a number of important areas of research; mental and physical health, child abuse and neglect, alcohol and drug use, juvenile delinquency, disability, education and housing. We have a large number of research projects overlapping these areas of focus. This reflects the complex nature of many of the problems facing Australian children and youth, and highlights the strengths of this project to address these multi-sectoral issues. The questions can be grouped into two broad areas:

1) Improving the understanding of the child, family and community factors involved in the pathways to juvenile offending, child abuse and neglect, poor physical and mental health

outcomes, educational achievement and school attendance/suspension; and identification of required interventions to optimally influence pathways; and

2) Monitoring of outcomes and evaluation of existing initiatives and policies.

Developmental Pathways in WA Children Project (DPP)

Fiona Stanley [University of Western Australia (UWA), Telethon Kids Institute]; Helen Leonard [UWA, Telethon Kids Institute]; Nicholas de Klerk [UWA, Telethon Kids Institute]; Jianghong Li [Curtin University of Technology, WZB Social Science Research Center Berlin, Telethon Kids Institute]; Natasha Nassar [UWA, University of Sydney]; Stephen Zubrick [UWA, Telethon Kids Institute]; Catherine Taylor [UWA, Telethon Kids Institute]; Amanda Langridge [UWA, Telethon Kids Institute]; Cheryl Gwilliam [WA Department of the Attorney General]; James McMahon [WA Department of Corrective Services]; Ruth Shean [WA Department of Training and Workforce Development]; Alistair Jones [WA Department of Treasury]; Timothy Marney [Mental Health Commission WA]; Karl O'Callaghan [WA Police]; Sharyn O'Neill [WA Department of Education]; Grahame Searle [WA Department of Housing]; Ronald Chalmers [Disability Services Commission WA]; Jennifer Mathews [WA Department of Local Government and Communities]; Cliff Weeks [Department of Aboriginal Affairs WA]; Emma White [WA Department for Child Protection and Family Support]; Laura Miller [Data

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Linkage Branch (DLB) 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 (WA) children and youth.

To achieve this, researchers from the Telethon Kids Institute and UWA have been working in collaboration with 14 state government departments, including the WA Departments of Health, Education, Training, School Curriculum and Standards Authority, Child Protection and Family Support, Corrective Services, Local Government and 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 Kids Institute, to create a fantastic cost-effective research and policy planning/evaluation resource.

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 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, as well as their families and communities.

The DPP was made possible by generous cash and in-kind contributions made by our collaborating organisations and government departments, which has been matched by the Australian Research Council (ARC) through two consecutive ARC Linkage Project Grants.

The DPP 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.

Staff and students

Head of group

Dr Rebecca Glauert
BPsych (Hons), PhD
Program Manager

Research staff

Marcela Quintero
MBBS
Data analyst
Dr Melissa O'Donnell
BPsych (Hons), MPsych, DipEd, PhD

National Health and Medical Research Council (NHMRC) Research Fellow

Scott Sims

BSc, MBiostat

Data analyst

Postgraduate students

Janice Wong

BSc (Hons Psych)

PhD candidate

Glenn Pearson

BA (Education)

PhD candidate

Jocelyn Jones

BSc, MEpi

PhD candidate

Megan Bell

BA (Hons Psych)

PhD candidate

Miriam Maclean

BA (Hons Psych), MSc

PhD candidate

Nan Hu

BSc, MSc

PhD candidate

Research support

Melanie Hansen

BSc

Research assistant

Miriam Maclean

BA (Hons Psych), MSc

Research assistant

Theses passed

Dr Anna Ferrante

DipEd, BA (Mathematics), PhD

UWA

'Dimensions of delinquency: Exploring group differences in the prevalence and frequency of offending: A linkage-based study of offending in the Western Australian population'

Dr Desiree Silva

MBBS, MPH, FRACP, PhD

UWA

'Early risk factors of children diagnosed with attention deficit hyperactivity disorder and their education and justice outcomes'

Awards

Janice Wong

Telethon Kids Institute Travel Award

Megan Bell

Winner, Best Early Career Presentation

International Health Data Linkage Conference 2014

External Committees

International

GROUP NAME

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

Rebecca Glauert

Closing the Gap Clearinghouse Board

2013 – 2014

Local

Rebecca Glauert

Ngala Professional Advisory Committee

2011 – present

Rebecca Glauert

Western Australia Data Linkage Infrastructure Project Board

2014 – present

Rebecca Glauert

Western Australia Data Linkage Infrastructure Project Advisory Committee

2014 – present

Miriam Maclean

Perinatal Mental Health Services Research Committee

July 2010 – present

Miriam Maclean

Marce Society Conference Local Organising Committee

January 2011 – present

Desiree Silva

Head of Department Medical Advisory Committee (HOD/MAC)

Desiree Silva

Chair of the Royal Australasian College of Physicians

Desiree Silva

State Paediatric Implementation Plan

Janice Wong

The Australian Association of Cognitive Behavioural Therapy

December 2010 – present

Invited presentations

The DPP had its work presented at over 15 international, national and state conferences, meetings and forums in 2014, many of those presentations were invited. A list of the various presentations made at international, national and state conferences, meetings and forums is provided below.

Desiree Silva

'Long term educational disadvantage by gender for children with ADHD'

Eunethydis Conference

Istanbul, Turkey

May 21-24, 2014

Desiree Silva

'Early life course for children and adolescents diagnosed with ADHD'

55th Annual Meeting of the Japanese Society for Child and Adolescent

October 2014

Shizuoka, Japan

Fiona Stanley

'Science with a Soul: data to action for health child development'

International Health Data Linkage Conference

April 28, 2014

Vancouver, Canada

Fiona Stanley

'From data to wisdom: using data for health'

Measuring Health Outcomes to Inform Policy Conference

May 27, 2014

Melbourne, Australia

Fiona Stanley

'Population monitoring as a strategy for improved early child development: progress and new challenges'

Human and Early Learning Partnership (HELP)

August 30, 2014

Vancouver, Canada

Fiona Stanley

'How population monitoring has improved child development outcomes'

Louisa Alessandri Memorial Fund Oration Evening

August 11, 2014

Perth, Australia

Janice Wong

'Using data linkage to determine the risk factors associated with children being diagnosed with a mental health disorder'

International Health Data Linkage Conference 2014

Vancouver, Canada

April 28-30, 2014

Megan Bell

'Predictors of vulnerability and risk on the Australian Early Development Index'

International Health Data Linkage Conference 2014

Vancouver, Canada

April 30, 2014

Megan Bell

'How do individual, family and neighbourhood characteristics influence children's early development and academic achievement?'

Aboriginal Health CRE

June 2014

Megan Bell

'How do individual, family and neighbourhood characteristics influence children's early development and academic achievement?'

Community Expo, Telethon Kids

GROUP NAME

Institute

July 10, 2014

Perth, Australia

Melissa O'Donnell, Marni Brownell,
Miriam Maclean, Scott Sims & Ruth
Gilbert

'Entering out-of-home care during
childhood: Cumulative incidence study
in two developed countries'

20th International Society for the
Prevention of Child Abuse and Neglect
International Congress

September 14-17, 2014

Nagoya, Japan

Melissa O'Donnell, Miriam Maclean,
Scott Sims, Helen Leonard, Vera
Morgan & Fiona Stanley

'Linking data for child welfare research
- Using linked child protection and
mental health to investigate mental
health diagnoses and child protection
risk'

20th International Society for the
Prevention of Child Abuse and Neglect
International Congress

September 14-17, 2014

Nagoya, Japan

Miriam Maclean, Cate Taylor & Melissa
O'Donnell

'Educational outcomes of children in
contact with the child protection system'

20th International Society for the
Prevention of Child Abuse and Neglect
International Congress

September 14-17, 2014

Nagoya, Japan

Nan Hu

'Parental psychiatric disorders and
children's deliberate self-harm (DSH) in
adolescence'

International Health Data Linkage
Conference 2014

Vancouver, Canada

April 30, 2014

Rebecca Glauert

'The importance of using data in
decision making: The Developmental
Pathways Project as an example'

National Elder Abuse Conference

September 2014

Perth, Western Australia

Rebecca Glauert

'Multi-agency data linkage - You CAN
do it!'

International Health Data Linkage
Conference

May 2014

Vancouver, Canada

Rebecca Glauert

'Linking data to build an evidence base:
The WA Developmental Pathways
Project'

University of Southern California

February 2014

Los Angeles, California

Active research collaborations

The DPP 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 departments, including those led by Professor Jablensky ('Pathways of risk from conception to disease: A population-based study of the offspring of women with bipolar disorder and schizophrenia'); Associate Professor 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').

The DPP is currently assisting the WA Mental Health Commission in an evaluation of their 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.

Investigators from the project also have an ongoing collaboration with Professor Ruth Gilbert and her team at the Institute of Child Health, University College London.

A systematic review was finalised

looking at the wellbeing and developmental health outcomes for maltreated children who have been in out-of-home care versus those who have not. A comparative study of trends was also conducted in relation to intentional and unintentional injury admissions associated with alcohol in youth in Western Australia and England.

In addition, researchers were involved in a cross-country comparison on neonatal drug withdrawal syndrome using hospital administrative data in England, the USA, Western Australia and Ontario, Canada.

Active involvement with the community

The Telethon Kids Institute recognises the central role of health consumers and community members in its research. Our aim is to develop partnerships in which consumers, community members and researchers work together to make decisions about research priorities, goals, methodologies, questions and dissemination of results.

The DPP has a Consumer and Community Reference Group (CCRG) which comprises of members for the community who have an interest in our topics of research. This groups meets four times a year and provides advice, interpretation and expertise to our research projects.

The CCRG was established to provide researchers with ongoing support

GROUP NAME

and advice and also has an oversight role for governance, standards and practices relating to the project from a community perspective.

Child abuse and neglect

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 DPP.

Melissa's research uses longitudinal population data provided through the DPP. 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.

Miriam Maclean

Miriam McLean is completing her doctorate on the DPP.

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 the WA Departments of Child Protection and Family Support,

Health, Education and Disability Services Commission through the DPP, to conduct a longitudinal analysis of prospective data from a large cohort of children.

Currently, WA 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

Glenn Pearson

Glenn Pearson, a Noongar from WA and the Manager of Aboriginal Health Research at Telethon Kids Institute, is completing his doctorate on the DPP.

His qualitative research project explores how the delivery of health, education and child protection services provided by the WA State Government to Aboriginal clients is mediated by the perceptions non-Aboriginal and Aboriginal people hold of themselves and each other in the provision and receipt of these services.

Juvenile offending

Dr Anna Ferrante

Anna Ferrante is an Associate Professor at the Centre for Data Linkage (CDL), Curtin University, formerly a Research Associate Professor at the Crime Research Centre, UWA.

As part of the DPP, Anna undertook a population-based study of the dimensions and development of delinquency in WA children.

The aim of the project was 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.

Jocelyn Jones

Jocelyn Jones is completing her doctorate through the DPP.

Jocelyn's 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

Dr Desiree Silva

Dr Desiree Silva is a paediatrician, and Professor of Paediatric Medicine at Joondalup Health Campus and UWA.

Desiree commenced a PhD through UWA and the Telethon Kids Institute on the risk factors and outcomes of children and adolescents diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) in WA.

Her PhD project uses longitudinal population data provided through the DPP. 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

Janice Wong

Janice is completing her combined Masters and doctorate through the DPP. Her project is titled 'The relationship between educational and mental

GROUP NAME

health outcomes for Western Australian children: A longitudinal population study.’

Using linked longitudinal population data provided through the DPP, this project 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 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.

Nan Hu

Nan Hu is completing his doctorate through the DPP. His project is titled ‘An investigation of the developmental pathways to hospitalised 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 hospitalisations in young people aged 10-30 years in WA and 2) To investigate how specific biological, psychological and social factors at the child, family, school and community level interact to

influence the developmental pathways to DSH related hospitalisation among young people. This will be achieved by undertaking five sub-studies 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

Megan Bell

Megan Bell is completing her combined Masters and PhD through the DPP and UWA.

Megan’s project is titled ‘How do individual, family and neighbourhood characteristics influence children’s early development and academic achievement? A linked data population study’ and aims to examine how early childhood development is related to educational achievement.

Using a linked data approach, Megan 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 Megan 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 Census (AEDC), which is a nation-wide assessment which gives an indication of child development at age 5.

Megan will also examine whether children's scores on the AEDC 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 WA, which will enable the development of interventions targeting the most vulnerable groups.

Awards

Megan Bell. Winner best Early Career Presentation, International Health Data Linkage Conference 2014, Vancouver, Canada, April 30, 2014.

External Committees

International

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

Rebecca Glauert. Closing the Gap Clearinghouse. Board member- 2013 to 2014

Local

Rebecca Glauert. Ngala Professional Advisory Committee (2011 – present)

Rebecca Glauert. Western Australia Data Linkage Infrastructure Project

Board (2014 – present)

Rebecca Glauert. Western Australia Data Linkage Infrastructure Project Advisory Committee (2014 – present)

Miriam Maclean. Perinatal Mental Health Services Research Committee (July 2010 – present)

Miriam Maclean. Marce Society Conference Local Organising Committee (January 2011 – present)

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

Janice Wong. The Australian Association of Cognitive Behavioural Therapy (December 2010)

Other notable achievements

In 2014, the DPP had a paper published in the Lancet Psychiatry investigating the link between ADHD and juvenile offending, and has over 30 other papers published from the grant, with several more under review or under commencement.

A list of all papers published in 2014 is provided below.

Cooper, M. N., McNamara, K. A., de Klerk, N. H., Davis, E. A., & Jones, T. W. (2014). School performance in children with type 1 diabetes: a contemporary population-based study. *Pediatric Diabetes*. doi: 10.1111/pedi.12243

GROUP NAME

Eitelhuber, T., & Davis, G. (2014). The custodian administered research extract server: "improving the pipeline" in linked data delivery systems. *Health Information Science and Systems*, 2(6).

Eitelhuber, T., Davies, G., Rosman, D., & Glauert, R. (2014). Western Australia unveils advances in linked data delivery systems. *Australian and New Zealand Journal of Public Health*, 38(4), 397-398.

Silva, D., Colvin, L., Hageman E., & Bower C. (2014). Environmental risk factors by gender associated with Attention Deficit/Hyperactivity Disorder. *Pediatrics*, 133(1), e14-e22.

Silva, D., Colvin, L., Hageman, E., Stanley, F., & Bower, C. (2014) Children diagnosed with attention deficit disorder and their hospitalisations: population data linkage study. *European Child & Adolescent Psychiatry*, 23(11), 1043-1050.

Silva, D., Colvin, L., Glauert, R., & Bower, C. (2014). Contact with the juvenile justice system in children treated with stimulant medication for attention deficit hyperactivity disorder: a population study. *Lancet Psychiatry*, 1(4), 278-285.

Silva, D., Houghton, S., Hagemann, E., Jacoby, P., Jongeling, B., & Bower, C. (2014). Child Attention Deficit Hyperactive Disorder comorbidities on family stress: effect of medication. *Community Mental Health Journal*, 51(3), 347-353.

Silva, D., Houghton, S., Hageman, E., & Bower, C. (2014). Comorbidities of Attention Deficit Hyperactivity Disorder: Pregnancy risk factors and parent mental health. *Community Mental*

Health Journal.

We are also conducting an economic analysis of the cost of pre-term birth, which is providing an increased burden on the health system.

We are also in the process of developing an online child Atlas using linked data, which will provide an online mapping tool for researchers and government.

We now employ three full time staff at the WA Department of Health in the DLB. These staff have assisted in the linkage of new datasets, developed a new server which will significantly reduce the burden of data linkage on data custodians and acted as a liaison point between researchers and custodians in the Department of Health.

We have now established a world class data linkage resource, which is the largest in Australia, and arguably, the world. We are leading the way on how to link cross-agency data, and have been invited to present all over the world.

List of Projects

We currently have 26 projects in various stages of completion using DPP data and skills.

Furthermore, we are being approached by national and international groups to access our resource.

A list of the various projects being undertaken by the DPP is provided below. All projects listed are expected to be completed by 2016 at the latest.

1. Project: The relationship between education and mental health outcomes for Western Australian children: a longitudinal population study;
2. Project: Preterm birth and developmental disorders: trends, outcomes and antecedents including hospitalisation patterns and long-term health and social outcomes;
3. Project: Public health approach to child abuse and neglect: antecedents and outcomes;
4. Project: Survival, hospitalisations and school achievement for children born with cleft lip and palate in Western Australia, from 1980 to 2010;
5. Project: An investigation of the developmental pathways to hospitalised deliberate self-harm behaviours (DSH) among young people: a birth cohort study using cross-jurisdictional linked data in Western Australia (WA);
6. Project: Promoting positive perinatal mental health, parenting, cultural and spiritual wellbeing, and resilience in young Aboriginal parents residing in two locations in Western Australia;
7. Project: The relationship between diet and educational outcomes in a cohort of Western Australian children;
8. Project: Alcohol and pregnancy: The impact of low to moderate maternal alcohol consumption on child health and developmental outcomes;
9. Project: Investigating the effect of maternal alcohol use disorder on the health and use of hospital services of the mothers and their offspring and social outcomes of the children including educational, juvenile justice and child protection outcomes;
10. Project: Triple P Parenting Program evaluation;
11. Project: Hot-spotting for juvenile offenders, risk factors and liquor outlets;
12. Project: Towards prevention – A population health approach to child abuse and neglect: A measurement model and the identification of antecedent causal pathways;
13. Project: Social and racial inequalities in birth rates and infant outcomes in Western Australia;
14. Project: On the dimensions and development of juvenile delinquency. A population-based study of the prevalence and frequency of offending and the influence of individual, family and community factors on delinquency in Western Australian children;
15. Project: 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;
16. Project: An evaluation of Supported Accommodation Services in Western Australia including impact over time on mental health outcomes and identification of the most effective/

GROUP NAME

efficient service delivery models;

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

18. Project: 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 type 1 diabetes cohort;

19. Project: An exploration into the delivery of health, education and child protection services by the WA state government to Aboriginal clients in the Perth metropolitan and Geraldton regions;

20. Project: Community characteristics associated with Australian Early Development Index outcomes;

21. Project: Childhood developmental pathways to educational achievement in Western Australia: A multilevel data linkage study. Examining the community, family and child characteristics and their impact on a child's developmental and educational outcomes;

22. Project: A prevalence study on parents with intellectual disability and their children;

23. Project: Youth offending and traumatic brain injuries;

24. Project: Mapping of Ngala call centre clients to assist with identifying high risk and high need areas;

25. Project: Maternal schizophrenia and bipolar disorder - an investigation of children's outcomes.

26. Project: Modelling linked population data to understand and improve long-term outcomes for children of incarcerated mothers to reduce social and economic impacts

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.

Sources of Fine Particulate Matter and Risk of Preterm Birth in Connecticut

Gavin Pereira, Michelle L. Bell, Hyung Joo Lee, Petros Koutrakis, and Kathleen Belanger

Pereira, Gavin, et al. "Sources of fine particulate matter and risk of preterm birth in Connecticut, 2000–2006: a longitudinal study." *Environmental health perspectives* 122.10 (2014): 1117.

The aim of this study was to assess whether anthropogenic sources are

associated with risk of preterm birth, comparing successive pregnancies to the same woman. Birth certificates were used to select women who had vaginal singleton live births at least twice in Connecticut during 2000–2006 (n = 23,123 women, n = 48,208 births). We procured 4,085 daily samples of fine particulate matter on Teflon filters from the Connecticut Department of Environmental Protection for six cities in Connecticut. Filters were analyzed for chemical composition, and Positive Matrix Factorization was used to determine contributions of sources of fine particulate matter. Risk estimates were calculated with conditional logistic regression, matching pregnancies to the same women. We identified fine particulate matter attributable to dust, motor vehicle emissions, oil combustion, and regional sulphur. There was insufficient evidence to suggest that sources were statistically significantly associated with preterm birth. However, elevated central estimates and previously observed associations with mass concentration motivate the need for further research. Future studies would benefit from high source exposure settings and longitudinal study designs, such as that adopted in this study.

Research Support

Gavin Pereira was supported by an NHMRC Early Career Fellowship (1052236). NHMRC Program Grant (572742).

Fine Particulate Matter and Risk of Preterm Birth in Western Australia

Investigators: Gavin Pereira, Michelle L. Bell, Kathleen Belanger, Nicholas de Klerk

“Fine Particulate Matter and Risk of Preterm Birth and Pre-Labor Rupture of Membranes in Perth, Western Australia 1997–2007: A Longitudinal Study.” *Environment International* 73 (2014): 143-149.

Our recent longitudinal study reported an association between fine particulate exposure and preterm birth in a US cohort. We applied the same design to an Australian cohort to investigate associations with preterm birth and pre-labor rupture of membranes. From 287,680 births, we selected 39,189 women who had singleton births at least twice in Western Australia in 1997–2007 (n = 86,844 births). Analyses matched pregnancies to the same women with conditional logistic regression. Risk of pre-labor rupture of membranes was greater for pregnancies with elevated fine particulate exposure in the second trimester than were other pregnancies to the same Australian women at lower exposure. There was insufficient evidence for an association with preterm birth, indicating that a longer time period might be needed to observe an association if a causal effect exists in Western Australia.

Research Support

Gavin Pereira was supported by an NHMRC Early Career Fellowship (1052236). NHMRC Program Grant (572742).

Fine Particulate Matter and Risk of Preterm Birth in Connecticut

Investigators: Gavin Pereira, Kathleen Belanger, Keita Ebisu and Michelle L. Bell

“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)

Fraser Mustard Centre

At the Telethon Kids Institute (Adelaide Team), a key component of our work continues to include the Australian Early Development Census (AEDC – formerly the Australian Early Development Index) research program, an Australian Government backed commitment that measures children’s development in communities across the nation. The AEDC 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.

Australian Early Development Census (AEDC)

Sally Brinkman, Tess Gregory, Angela Kinnell, Lydia Braunack-Mayer, Alanna Sincovich

The Australian Early Development Census (formerly the Australian Early Development Index or 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 AEDC 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 AEDC was completed nationwide for the first time with the Australian Government providing \$21.9 million for the implementation of the AEDC 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 AEDC 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 and Training awarded \$1.5 million in funding directly to the Telethon Kids Institute to explore the 2009 and 2012 AEDC 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 AEDC 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

GROUP NAME

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 AEDC. The Social Research Centre, Melbourne, is managing the AEDC data.

Provision of Engagement Services for the AEDC

Sally Brinkman, Yasmin Harman-Smith, Tess Gregory, Melanie Sander, Alanna Sincovich

In 2014 the Telethon Kids Institute was engaged on a three year contract to provide support services in relation to the Australian Early Development Census (AEDC). Within this scope of works, support services are provided to both the Department of Education and Training (Canberra) and the eight AEDC State and Territory Coordinators and their support staff across Australia.

The Institute's AEDC support team provides professional development opportunities, strategic advice and support, and develops AEDC engagement resources to support

the implementation and utilisation of the AEDC by community, schools, governments and researchers. The team also manages an online learning portal and forum for AEDC coordinators, delivered a National Conference focused on the AEDC, and coordinates monthly national teleconference and quarterly national meetings.

Funder of the Project: Federal Government, Department of Education and Training

Australian Early Development Census (AEDC) Pilot Communities – Exploring results over time.

Sally Brinkman, Tess Gregory, Angela Kinnell, Lydia Braunack-Mayer

The Australian Early Development Census (AEDC - formerly the Australian Early Development Index) provides a snapshot of child development at school entry for all of the children living in Australia once every three years. In 2015, the third census will be completed providing the first opportunity to explore trends in child development for Australia.

Prior to the national census, about 60 communities across Australia were involved in early pilot research using the same instrument. The current project aims to provide these communities with comparable data from the pilot (2004-2008) and the first two census collections (2009 and 2012), so that they can compare the child development outcomes in their communities over time. This project has a strong research translation

component by exploring a range of different ways to present trend data on the AEDC over time, which will inform the development of community reports using 2009, 2012 and 2015 AEDC national census data.

Funders of the Project: Department of Education and Training (Australian Government)

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. There are presently 42 Children's Centres across South Australia. Children's Centres are generally 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 process and impact evaluation of South Australian Children's Centres. The mixed methods evaluation commenced in 2012 and the first stage of qualitative works were completed in 2014. An interim report on the qualitative findings has been produced and is available on the Fraser Mustard Centre website. A survey of staff working in Children's Centres, Service Providers working with Children's Centres, and families using Children's Centres was undertaken during 2014. The survey results will be reported alongside service usage data, which is being collected systematically in Centres for the first time in 2015. The evaluation is due to be completed by July 2016.

Funder of the Project: Government of South Australia, Department for Education and Child Development

Conceptual paper on screening and assessment in early childhood and at school entry

Sally Brinkman, Simon O'Brien

South Australia, through the Department for Education and Child Development, has been tasked with leading a national project that will provide a comprehensive picture of the range of data collections and specific screening and assessment tools used across

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health, early childhood and education sectors to consider ways in which these tools can support practice, policy development and national research priorities. The Department has engaged the Telethon Kids Institute to undertake an initial state specific review that will provide a foundation for this project.

The overall objectives of the evaluation are to: 1) To consider what developmental domains (and family factors that influence) should be screened and assessed to best respond to learning and development needs, 2) When these measures would be best implemented taking into consideration sensitive periods in development, 3) Current contact points for screening and assessment in South Australia. Using the findings from these reviews, a range of recommendations will be formulated for consideration by the Department.

Funder of the Project: South Australian 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.

The evaluators have worked with the program providers to establish a database to collect administrative and outcomes data for clients of the service. The Strong Start program has

been established for the first time, thus the evaluators have worked closely with the program providers to design an evaluation that enables them to respond to implementation challenges as the program becomes imbedded as well as to measure what difference the program is making for clients and their infants. The evaluation uses a mixed-methods design to measure both process and impact.

To date the evaluators have conducted interviews with service providers in the program catchment area who might refer clients into the service to enable Strong Start to address recruitment difficulties. The next stage of works will involve interviews with Strong Start staff and clients to identify elements of the program that are working well and those that require refinement. A final stage of works will examine early client outcomes with utilisation of administrative and outcomes data. The evaluation is due for completion in February 2016.

Funder of the Project: Government of South Australia, Department for Education and Child Development

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 used novel speech recognition technology (Language Environment Analysis: LENA) to unobtrusively measure the language environment of the child in the home. This was a pilot aimed to trial recruitment, the consent forms and participant families' level of comfort with LENA. In addition, the study enabled us to test the LENA software and output.

The study used predominantly qualitative feedback from caregivers, with cogency checks achieved through quantitative analysis where applicable. Participation involved infants and toddlers wearing a specialised recording device for a 16 hour duration to collect audio environment and social data. The recording device was worn inside a small front pocket of specially designed children's clothing for the day, except whilst napping or bathing. Participating caregivers completed a series of questionnaires in addition to a complimentary time-use diary for the recording day.

The recording device processed the audio from each 16 hour recording period into five audio environment categories; (1) Meaningful speech (near and clear to the child), (2) Distant speech, (3) TV and electronic sound, (4) Noise and (5) Silence and background. For meaningful speech, the LENA software automatically quantified two measures of caregiver input, comprising of Adult Words and Conversational Turns. The software also measured child input through quantifying child

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vocalisations. Tallies for each of these three measures were available to be viewed and/or exported in 5-minute, hourly or daily increments.

As a result of the pilot we are confident in LENAs ability to discriminate between background noises (such as TV and radio) and between different adults and children. LENA has been able to provide accurate assessment of all three key variables (Parent Talk, Parent-Child Talk and Child Talk). Feedback from the families from the pilot was positive, with participants finding it extremely easy and stress free to use. Children liked the clothing choices, and parents commented on how quickly the children and they themselves forgot about the recording device. Findings from this study provide the preliminary data and experience to guide future large-scale use in South Australia.

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

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. 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.

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).

Researchers completed a pilot project in 2013, measuring the wellbeing of approximately 6,000 children across South Australia and Victoria in the middle years of school in order to provide summary information back to policy makers, schools and communities about the health and wellbeing of their children. In 2014, DECD completed a second round of data collection involving almost 18,000 children, including schools and students which participated in the 2013 research trial, allowing the accuracy of data to be explored further and to provide these schools with two data points. Participating schools have now received their school report containing data on

student's self-reported wellbeing.

In 2013 the MDI received additional financial support through an ARC Linkage grant of \$223,000 for 2013-2015. The grant provides further funding to establish the validity of the MDI in Australia, explore the international comparability of the instrument between Australian and Canada, and culturally adapt the MDI for Australian Aboriginal children, by leveraging off the MDI data collected.

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 aims 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, researchers at the Fraser Mustard Centre have developed an Evaluation

Plan including a mixed method approach with quantitative and qualitative research methodologies for evaluation implementation.

Key evaluation questions 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?

The next stage of this project requires linked data to be obtained from SANT DataLink – once approvals are obtained, researchers can begin data analysis.

Funder of the Project: Government of South Australia, Department for Education and Child Development

Thriving in Adversity

Sally Brinkman, Tess Gregory, Britney Keech, Alanna Sincovich

Both NAPLAN and Australian Early Development Census (AEDC) 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 communities that are performing higher than would be predicted by statistical models. This project sought to explore the characteristics of these 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 involved both quantitative and qualitative analysis to better understand what is driving this success. Researchers developed reliable statistically risk adjusted (value added modelling) techniques to identify the genuine high performing statistical outliers. As a result, eight South Australian communities were selected for investigation – four of which were performing as expected in adversity, and four that were thriving in adversity.

In addition to the quantitative analyses, researchers carried out desktop analysis and community consultation. We explored the programs and services that were available for young children and their families in each of the eight communities and aimed to identify factors that may have promoted resilience and improved child development and educational outcomes. Thriving communities had a tendency to work collaboratively across different agencies and sectors, with co-location of key early childhood education services. Thriving communities tended to provide early literacy programs to young children by a trained facilitator through their local libraries, had more playgroups and a much higher proportion of children attending playgroups. Community involvement emerged as an important feature of thriving communities,

however, differences in health services and playgrounds were not notable. The full report can be found on the Fraser Mustard Centre website.

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, Simon O'Brien

The Australian Early Development Census (AEDC, formerly the Australian Early Development Index) is undertaken once every three years by the Department of Education and Training, Canberra as a progress measure of future human capital for the Council of Australian Governments. The AEDI has been completed in 2009 and 2012, and results for South Australia reveal patterns of child development across the state. Although simple descriptive statistics are produced and mapped data for communities are available via the national AEDC website – the AEDC results had 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 AEDC results in SA. Specifically, this project aimed to:

- Determine if the areas where Children's Centres and the Learning Together program is operating are showing a different pattern of AEDC

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?
- Investigate the pattern which saw a 6 percentage point drop in the percentage of Aboriginal children who spoke a language other than English in the AEDC between 2009 and 2012.
- 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.

The final project report was delivered to DECD in early 2015, and will soon be made available on the Fraser Mustard Centre website.

Funder of the Project: Government of South Australia, Department for Education and Child Development

Evaluation of the Community Playgroup Program

Sally Brinkman, Yasmin Harman-Smith, Tess Gregory, Alanna Sincovich

At the request of Playgroup Australia, in 2014 researchers at the Telethon Kids Institute have been engaged to conduct an evaluation of the Community Playgroup Program across Australia. Community playgroups, substantially the most common form of playgroup, are regular gatherings for parents

and young children under school age, which generally meet once a week for one or two hour sessions. They provide an opportunity for children to learn through unstructured play and for parents to develop social networks and improve parenting skills. Playgroup attendance is likely to impact child development through several pathways, there is, however, limited national and international research quantifying the specific impact of playgroups on childhood development and wellbeing.

The overall objectives of the evaluation are to: 1) Analyse and describe the Community Playgroup Model – how it sits in the current policy environment looking at its strengths and weaknesses within Australia and internationally, 2) Examine and analyse the factors which have resulted in a significant decline of Community Playgroups since 2006, 3) Make recommendations about future policy options for Community Playgroups. The evaluation employs a mixed-methods research design utilising both qualitative and quantitative data to address the research aims.

Funder of the Project: Playgroup Australia

Fraser Mustard Centre PhD Top-Up Scholarships

Supervisors: Sally Brinkman and 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

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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.

The second Fraser Mustard Centre Top-Up Scholarship was awarded in 2014 to Ms Catherine Johnson. Catherine is completing a PhD in the School of Psychology at Flinders University. Her project is titled: Mindfulness in Schools: A transdiagnostic prevention programme.

Veronica Smyth has been awarded the third Fraser Mustard Centre Top-Up Scholarship. Veronica will commence her PhD in 2015 in the School of Population Health at the University of Adelaide, and will conduct a project examining inequalities in communication between children and their caregivers. Veronica's PhD work will make use of innovative speech recognition technology and linked data

to investigate influences on children's capability formation, particularly in relation to language development.

Funder of the Project: Government of South Australia, Department for Education and Child Development

Health Promotion and Education Research and Translation Group

Winthrop Professor Donna Cross and her team relocated to the Telethon Kids Institute in March 2014 from Edith Cowan University. Their research focuses on the development and evaluation of innovative school and community-based interventions to enhance the emotional and social wellbeing of children and adolescents.

Mental Health Research

Promotion of mental health and wellbeing in young people

Investigators: Donna Cross, Stephen Zubrick (Telethon Kids), Marilyn Campbell (QUT), George Patton (UniMelb), Michael Rosenberg (UWA), Phillip Slee (Flinders), Barbara Spears (UniSA)

The Collaborative Research Network program is part of a suite of initiatives established by the Australian Government to reform higher education teaching, learning, research and research training. The

ECU-led Collaborative Research Network focuses on growing research excellence at the University through partnership and engagement. It aims to create world-class research capacity and outcomes through collaborative partnership with nine universities across Australia.

The sub-project led by Professor Donna Cross has resulted in the development of a national group of researchers working collaboratively to promote the mental health and wellbeing of young people. This group collaborates on research publications, research proposals, supervision of higher degree by research students and the provision of research training schools for early career researchers. The research group includes:

- Associate Professor Michael Rosenberg, University of Western Australia
- Professor George Patton, University of Melbourne; Paediatrics Royal Children's Hospital
- Professor Phillip Slee, Flinders University
- Dr Barbara Spears, University of South Australia
- Winthrop Professor Steve Zubrick, University of Western Australia; Telethon Institute for Child Health Research
- Professor Marilyn Campbell, Queensland University of Technology

This project involves the development

of a collaborative group of researchers across Australia working to enhance the mental health and wellbeing of young people. Activities have included joint research proposals, publication, supervision of research students, and research training seminars and workshops for early career researchers.

Funders of the project: Collaborative Research Networks (CRN) Program, Department of Innovation, Industry, Science and Research

Enhancing adolescent mental health through positive education

Investigators: Dianne Vella-Brodrick (UniMelb), Nikki Rickard (Monash), Donna Cross (Telethon Kids), John Hattie (UniMelb), Justin Robinson (Institute Positive Psych), Christine King (UniQLD)

Mental disorders are the single greatest burden of disease for adolescents with reports of around 1 in 4 people aged 16-24 years experiencing mental illness in Australia. Positive Education in schools may offer feasible solutions for reducing the escalating incidence of mental illness and promoting engaged learners, flourishing and pro-social behaviours among young people.

This project involves evaluation and identification of key features of the Positive Education Program at Geelong Grammar, and the adaptation of the program to suit public schools. Program evaluation will utilize momentary sampling and physiological indicators, to complement focus groups and self-report measures.

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Positive education is a preventative, strengths-based approach to address the mental health needs of young people in schools. This project uses innovative methods to examine the contribution of positive education to adolescent mental health, and to social and learning outcomes.

Funders of the project: Australian Research Council

Bullying, Cyberbullying and Aggression Research

Testing a comprehensive targeted intervention to reduce student bullying ('Beyond Bullying')

Investigators: Donna Cross (Telethon Kids), Marilyn Campbell (Qld Uni Tech), Phillip Slee (Flinders), Ken Resnicow (University of Michigan), Christina Salmivalli (University of Turku)

Peer bullying is a stubborn social problem. Despite attention to the problem by schools, communities and researchers, bullying continues to be highly prevalent in Australian schools. Researchers have found that working with the whole school to address cultures that support bullying has some effect, but further work is needed to develop strategies to prevent these behaviours. To date, one of the chief challenges has been stopping bullying at the source: the young people who engage in repeated or severe bullying behaviours.

The Beyond Bullying project is trialing an innovative approach known as Motivational Interviewing (MI).

Motivational Interviewing is particularly powerful when changing the problem behaviour elicits resistance from the person engaging in this behaviour. MI has previously been successfully used in counselling and guidance settings to help young people change and resolve problems with alcohol and substance use, eating disorders, gambling problems, and, most importantly, to reduce violent behaviour.

The study examines the efficacy of MI as a targeted intervention in conjunction with the Friendly Schools Plus whole-school bullying prevention program, which is an evidence-based program that helps limit problems with bullying. The study is being conducted at the Telethon Kids Institute, Western Australia, by the lead investigator Winthrop Professor Donna Cross and project director Dr Kevin Runions.

The Beyond Bullying project is being trialed in Western Australian schools as a way to reduce the prevalence and impact of bullying. The project involves counselling young people who are identified as bullying others with an approach known as Motivational Interviewing, which is used to enhance their motivation to change their behaviour. In addition, the 'Friendly Schools Plus' program is used to provide schools with resources and strategies to prevent and address bullying behaviours and attitudes among all students.

Funders of the project: NHMRC (Targeted Mental Health Call)

PAVe (Preventing Anxiety and Victimisation through education)

Investigators: Ron Rapee (Macquarie), Donna Cross (Telethon Kids), Kay Bussey (Macquarie), Caroline Hunt (UniSyd), Jennifer Hudson (Macquarie), Cathy Mihalopoulos (Deakin), Clare Roberts (CurtinUniTech), Nick Titov (Macquarie)

The study is being conducted by the Centre for Emotional Health at Macquarie University under the leadership of Professor Ron Rapee and with Professor Donna Cross at the Telethon Kids Institute, University of Western Australia.

This study will evaluate the effectiveness of two evidence-based approaches to support students who have been frequently targeted by bullying in primary schools:

- Friendly Schools Plus: a strengths-based, whole-of-school program designed to enhance students' social and emotional learning and foster the prevention of bullying behaviours;
- Cool Kids: Taking Control: a strengths-based, targeted program designed to build resilience in those children who have been targeted by bullying behaviours

These programs will help schools reduce all forms of bullying by developing students' social and emotional learning, building positive peer relationships, and empowering students to cope successfully with difficult situations.

PAVe is an exciting new research intervention project being conducted in over 100 NSW and Western Australian primary schools, which aims to support students who have been frequently bullied. The project will help schools reduce all forms of bullying by developing students' social and emotional learning, building positive peer relationships, and empowering students to cope successfully with difficult situations.

Funders of the project: NHMRC, Australian Government Department of Education and Macquarie University

Building school capacity to reduce social aggression among students

Investigators: Donna Cross (Telethon Kids), Anjie Brook (WA Dept Education), Elizabeth Healy (WA Dept Education), Rob Nairn (ECU), David Mander (ECU), Lydia Hearn (UWA), Sharyn Burns (Curtin), Natasha Pearce (ECU)

The Strong Schools Safe Kids research project was funded by Healthway under a 'research to practice' grant that aimed to support the translation of current evidence of school-based bullying prevention interventions into real world practice. Whilst schools have access to a national Australian framework of action for safe schools that supports a whole-school approach, and there exists a greater understanding of the barriers and enablers to whole-school implementation, schools still report implementation challenges limiting their capacity to achieve positive outcomes in policy and practice. This research

project aims to understand how schools in different contexts translate empirically supported policy and practices to prevent and manage student social aggression and bullying behaviours and how their capacity to implement these practices can be strengthened to promote sustainability and improve impact.

Four phases of 'Translational Formative Evaluation Research' recommended by O'Hara and colleagues (2013) were conducted including a synthesis of the research findings, an environment and policy context analysis, longitudinal mixed methods research with schools and consultation with key stakeholders over a five year period (2010 – 2014). The research findings were used to develop a systematic approach to whole-school implementation and capacity building in preparation for wider dissemination and implementation of an Australian evidence-based, whole-school bullying prevention intervention called Friendly Schools. Key learnings show that when schools undertake a systematic implementation process, capacity for whole-school change can be strengthened for great student impact.

The Strong Schools Safe Kids research project was funded by Healthway and aimed to develop supports for schools to improve their practices to prevent student bullying behaviours. Seven case study schools were observed over four years to see how schools used a new implementation process and tools to assess needs, select evidence-

based practices and implement change to address pastoral care support and bullying behaviours. Key learnings show that when schools undertake a systematic implementation process, capacity for whole-school change can be strengthened to improve positive social and emotional outcomes for students.

Funders of the project: Healthway

Cyber-aggression and cyber-victimization (CAV): A mixed-methods study of structural features and individual differences in online social information processing

Investigators: Kevin Runions (Telethon Kids), Danielle Law (Wilfred Laurier University), Jennifer Shapka (Uni British Columbia), Debra Pepler (York University)

Some experiences that may be interpreted as cyber-aggression and victimisation (CAV) may not, in fact, have been acts intended to harm, but are nevertheless interpreted as harmful and result in psychological harm. Interpreting the intent and emotional tone behind cyber-communications is a key digital skill, and one that can be challenging.

Our conceptual framework (Runions et al., 2012) systematically considers how the new technologies enabling online social networks might present distinct influences (i.e., opportunities and constraints) for aggression and victimization that are different from those afforded by traditional modes of communication. In this study, we

seek to analyze how interpretation of semantic content is influenced by the opportunities and constraints that arise via communicating over that medium.

A key structural property of the bulk of communication online is its text-only nature (Runions, Shapka, Dooley, & Modecki, 2012). As such, it provides few or no semantic information from body language (i.e., nonverbal cues) or tone of voice (i.e., paralinguistic cues). The use of emoticons (e.g., :) and jargon (e.g., LOL) aims to reduce this ambiguity, but research suggests that these can instead increase ambiguity, and instill an interpretation of sarcasm and condescension (Derks, Bos, & Grumbkow, 2007), which may in fact fuel interpretations of hostility. In all, this paucity of social semantic cues leaves online communication ripe for misinterpretation, including erroneously attributing hostility to benign but ambiguous communication.

The present study aims to better understand how this ambiguity operates in young people's interpretation and response to cyber-communication. A second phase addresses, via an experimental design, whether participants discern between intentionally harmful (exemplar) messages and intended jokes, and whether emoticon usage, the status of the sender (a popular acquaintance vs. an unpopular acquaintance), and the perceived audience for the communication (private or public) influence youth's interpretation and response to cyber-aggressive

communications.

Thus there is a skill in both crafting and interpreting digital communications, but it is a skill about which we know very little. The present research aims to increase our understanding of how youth navigate this ambiguity and their experiences in interpreting ambiguous but potentially hostile/ bullying communications, and to provide preliminary tests of a new conceptual model (Runions et al., 2012). The outcomes of this research would provide important directions for how best to prepare youth and their teachers and parents for the complexities of their digital lives, so that misinterpretation does not fuel psychological problems.

When communicating with one another online, young people rely on text-messages and other written communication, without being able to see one another or hear one another's voices. This reliance on text means that misunderstandings can arise that might be taken to be cyberbullying, even if they aren't really meant that way. This study provides a first look at how young people make sense of their online communications, and some key factors that might influence what they see as hostile or not.

Funders of the project: Social Sciences and Humanities Research Council (Canada)

'Cyber Savvy' Project

This body of research into sexting and electronic-image sharing is funded

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through two research projects:

Assessing the public health implications of higher risk online behaviours in young people

Investigators: Donna Cross, Therese Shaw (Telethon Kids), Rebecca Guy (UniNSW)

Funders of the project: Telethon-New Children's Hospital Research Fund

Students leading change to reduce sexting-related harm to young people

Investigators: Donna Cross (Telethon Kids), Therese Shaw (Telethon Kids), Rebecca Guy (UniNSW), Shirlee-Ann Knight (ECU), Karen Murcia (ECU)

Sexting is increasing in prevalence and beginning at increasingly younger ages among young people. It is linked to significant social, psychological and legal consequences for those who produce and who share this material with others. Very few of the cyber safety resources currently available in Australia have been developed with a comprehensive understanding of young people's sexting behaviour. This innovative four-phase mixed methods study not only addresses this new phenomenon but actively engages young people to determine and deliver authentic ways to reduce its prevalence and harms.

This study uses a three-stage exploratory sequential design in its formative stages, with qualitative data informing the development of a quantitative questionnaire, and then

these combined findings informing the development of the online intervention. Qualitative data exploring young people's understanding of online behaviour, including sexting, was collected from approximately 80 students through group activities and focus groups during a two-day student Cyber Leader Summit.

Findings from these qualitative data are being used to help refine items and scales measuring how and why young people interact with and respond to images in a cyber environment. Cyber Leaders and staff with experience in online educational materials development will use the qualitative and quantitative data to inform the development of the online resource. This resource will be implemented via schools in 2015. Student and teacher process (use and satisfaction) data will be collected using face-to-face teacher interviews, pre-post student survey, web metrics and Audio-CASI interviews with students.

Advisory stakeholder committees engaging young people, parents, school staff and policy makers are being recruited to facilitate and maximize translation validity of the resources developed, while also guiding the progress of this research.

Recent research suggests approximately a quarter of teenagers have sent nude or semi-nude images or videos of themselves via an electronic medium. The consequences of sexting include leaving an online digital trail that might affect future employment and

relationships; provide opportunities for blackmailing; humiliation if the image is shared further; and the resulting emotional trauma. This study aims to improve what we know about this behavior and help young people make safe and healthy decisions about the images they share. Young people's perspectives are being actively used to develop and test an online resource that will enable families, schools and other adults working with young people to respond more effectively to reduce sexting-related harms.

Funders of the project: Healthway and the Department of Education

Human Capability

Sugar Sweetened Beverage consumption by Australian children: Implications for public health strategy

Investigators: 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

The influence of long-term joblessness and separation of grandparents on grandchildren

Investigators: Kirsten Hancock and Stephen R. Zubrick, with Ben Edwards (Australian Institute of Family Studies)

We have understood for many years that family experiences such

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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.

ARC Centre of Excellence for Children and Families over the Life Course
#CE140100027

Multiple disadvantage across generations in Australia

Investigators: Kirsten Hancock, Francis Mitrou, Stephen R. Zubrick

Families are a critical pathway in the transmission of disadvantage. While the literature broadly focuses on parent-child transfers in understanding intergenerational disadvantage, further insight can be achieved by examining markers of disadvantage across multiple generations of the same family. Studies examining multigenerational

patterns of disadvantage are therefore valuable, but the availability of Australian data to investigate these patterns has been limited until recent years. With new data now available, this study will examine the experience of multiple disadvantages in two generations of Australian families, and how these experiences relate to the trajectories of children, the third generation. This work expands upon our initial projects that examined particular aspects of intergenerational disadvantage such as joblessness and family separation.

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#CE140100027

Playgroup participation and social support outcomes for mothers of young children

Investigators: Kirsten Hancock, Nadia Cunningham, David Lawrence, and Stephen R. Zubrick with David Zarb (Playgroup WA Inc).

The project used data from the Longitudinal Study of Australian children to examine friendship networks and social support outcomes for mothers according to patterns of playgroup attendance when their child was aged 3–19 months and 2–3 years. Compared mothers who participated at both time points, mothers whose child did not participate in playgroup at either age were significantly more likely to report having no support from friends when the child was 4–5 years and again at age 8–9 years. The results provide

evidence that (persistently) participating in a playgroup may be a protective factor against poor social support outcomes, and that socially isolated parents may find playgroups a useful resource to build their social networks.

Funders of the project: NHMRC program grant #572742.

Attitude, attendance and achievement: A longitudinal view of student development and participation in education over time.

Investigators: 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 than 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.

ARC Centre of Excellence for Children and Families over the Life Course
#CE140100027

Causes and consequences of student mobility in Australia

Investigators: Kirsten Hancock, Stephen R. Zubrick

Research shows that students who change schools are at greater risk of lower educational attainment and early dropout than less mobile students. While it is understood that there are many reasons, both positive and negative, that underpin unscheduled school transfers, all types of school moves are typically considered equal. This approach has led to inconsistent findings related to student mobility and how it relates to other student outcomes. In addition, our knowledge regarding the extent and nature of student mobility for Australian students is limited. The aim of this study is to provide an overview of student mobility in Australia using a nationally representative longitudinal cohort of Australian children, and to determine whether the different reasons underlying mobility are related to differences in progress over time.

GROUP NAME

ARC Centre of Excellence for Children and Families over the Life Course
#CE140100027

Sources of processed and refined foods in children's diets

Investigators: Wavne Ridders, Katherine Hafekost, David Lawrence and Stephen R. Zubrick

Public health agencies have consistently called for regulation of 'takeaway' food marketing, and access to these food outlets. The main reason is that food and beverages sourced from outside the home, such as those from 'takeaway' food outlets and restaurants, are considered to be contributors to the high prevalence of obesity and incidence of chronic disease in Australia and other Western countries. However, it is possible that highly processed and refined foods of poor nutritional quality, which are sourced from supermarkets, may be consumed in the home in equal or greater proportion to that of similar foods sourced from outside the home.

The aim of this study is to evaluate the proportion of children's diets that come from sources outside the home and to compare the nutritional value of those foods with that of highly processed and refined foods purchased from supermarkets and prepared inside the home. Using results from the National Children's Nutrition and Physical Activity Survey 2007, we will determine the proportional contribution (in terms of percentage of energy and number of meals) to children's diets from each

food source. We will also look at whether this varies according to the child's age group, sex or any other demographic characteristic.

Funders of the project: NHMRC program grant #572742.

Young Minds Matter: The Second Australian Child and Adolescent Survey of Mental Health and Wellbeing

Investigators: 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 was completed in April 2014. A final publication of survey results is due for release mid-2015.

The broad aims of the National Survey of Mental Health and Wellbeing initiative are to determine how many

Australians have 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).

Factors that promote child vocabulary in the early school years: Findings

from the Longitudinal Study of Australian Children and the Longitudinal Study of Indigenous Children

Investigators: Brad Farrant, Stephen R. Zubrick

Vocabulary knowledge is a critical component of school readiness. This project aims to investigate the factors that promote vocabulary development across early childhood for Indigenous and non-Indigenous children. So far this research has found that 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). 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 school entry. 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

GROUP NAME

Investigators: 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 and Literacy Development in the Longitudinal Study of Australian Children

Investigators: Cate Taylor, Stephen R. Zubrick, Daniel Christensen, David Lawrence, Francis Mitrou.

Our uniquely human capacity for language is one of the most important developmental accomplishments of childhood and is a tool for life. Young children acquire the language(s) spoken to them at home through everyday interactions and experiences with their caregivers. Neurobiology (including genetics) and the child's nurturance,

social interactions, shared activities, and input from caregivers shape the child's journey to acquiring the adult language system. The centrality of language to everything we do in life means that almost everyone has a theory about why most children acquire language with remarkable ease, while others do not. Recent discoveries about patterns and predictors of stability, change, improvement, and decline in children's language abilities in the first 10 years of life have led us to re-think some deeply held beliefs about language and literacy as well as the policies services and supports designed to support children's language and literacy development.

Funders of the project: NHMRC Program Grant #572742.

Twins and singletons with specific language impairment (Looking at Language)

Investigators: Catherine Taylor, Stephen Zubrick with Mabel Rice, Shelley Smith, Javier Gayan, and Hugh Catts

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 children and families overall.

The study has received 15-years continuous funding from the USA National Institutes (National Institute on Deafness and Other Communication Disorders). The project is a joint initiative between the Telethon Institute for Child Health Research and UWA and the USA's University of Kansas and University of Nebraska Medical Centre. All study participants and data collection is based in Western Australia.

Funders of the project: National Institutes of Health (RO1DC05226, P30DC005803, P30HD002528).

Future under threat: climate change and children's health

Investigators: 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

Investigators: 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.

Methods for engaging with the community in setting priorities for child health research

Investigators: Wavne Ridders, 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

Investigators: 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

GROUP NAME

all CAMHS units.

Funders of the project: WA Department of Health

Contribution of Indigenous cultural factors to survey response

Investigators: 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

Investigators: 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)

Investigators: Francis Mitrou, Daniel Christensen, Katherine Hafekost, David Lawrence and Stephen R Zubrick with Ilan Katz, Kristy Muir and Fiona Hilferty (The University of New South Wales), Rebecca Cassells, Alan Duncan (Curtin University)

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

Investigators: Cate Taylor, Sally Brinkman, Jasmin Harman-Smith and Daniel Christensen with Wietse van de Lageweg, Andrew Oakley (Tasmanian Department of Education)

The Tasmanian Child and Family Centre model is a community level early childhood integrated service model to improve the educational outcomes, health, development and wellbeing of Tasmanian children (birth to 5 years). The Tasmanian Government announced the Child and Family Centre model in 2009 and 11 Child and Family Centres opened 2011-2013. The Tasmanian Department of Education is the lead agency for the Child and Family Centres. Tasmanian Child and Family

Centres are a new way of providing services and supports for families of young children. The services comprise universal services plus services based on the specific needs of a community. Services and supports work together to support children and parents. The services and supports for children and parents are all provided under one roof. The first Child and Family Centres in Tasmania opened in 2011. The key criteria for selecting Child and Family Centre communities were high need for services and support (based on socioeconomic area disadvantage); a high population of preschool age children; and high projected population growth. From the outset, community members have had a high level of control and responsibility for the design, implementation, and governance of Child and Family Centres.

The Tasmanian Child and Family Centres are designed to have a whole-of-community impact and the outcomes that Child and Family Centres want to achieve have already been documented in the Tasmanian Child and Family Centres Statewide Outcomes Framework. The Statewide Outcomes Framework was developed with input from communities so researchers know that these are the outcomes that the communities want. The aim of this project is to understand the impact of Child and Family Centres on three family outcomes from the Statewide Outcomes Framework:

1. Families are supported by and connected to their communities.

GROUP NAME

2. Parents have skills and knowledge to nurture their children.
3. Families have opportunities to participate in learning pathways.

Quantitative and qualitative methods and use of linked administrative data are being used to understand the impact of Child and Family Centres.

Funders of the project: Tasmanian Early Years Foundation

Development of the Adolescent Self Esteem Questionnaire

Investigators: 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

Investigators: 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

Systematic Review of the evidence for a relationship between trans-fatty acids and blood cholesterol

Investigators: Katherine Hafekost, Therese A O'Sullivan (Edith Cowan University), David Lawrence and Francis Mitrou

This review sought to identify literature, published between 2010 and 2014, relating to the consumption of TFA in the diet and associated changes in blood lipids, compare the outcomes of recent literature to the existing body of research, and evaluate the implications of these findings in an Australian and New Zealand context. When considering the existing body of literature, a one percent increase in TFA as a percentage of energy intake, was associated with a small but significant increase LDL, and decrease in HDL. However, there was no significant relationship between total cholesterol values and intake of TFA. Possible dose response relationships were identified. However, there was substantial variability in the reported blood lipid changes at TFA intakes of at and below one percent of energy intake. The results of the review suggest that current dietary guidelines and recommendations relating to intake of TFA in the Australian and New Zealand diet are appropriate. Ongoing monitoring of industry action and population intake of TFA is recommended to ensure levels of consumption remain low.

Funders of the project: Food Standards Australia New Zealand

Narrative review: The relationship between dietary trans-fatty acids and adverse health outcomes

Investigators: Therese A O'Sullivan (Edith Cowan University), Charlotte Wilson (Edith Cowan University), Katherine Hafekost, Francis Mitrou and David Lawrence

Existing evidence suggests that dietary intake of trans-fatty acids (TFA) is positively associated with risk of coronary heart disease and cardiovascular disease. In addition, it has been linked to increased risk of chronic conditions including cancer and type 2 diabetes. The narrative review aimed to build on existing risk assessment in relation to TFA intake and chronic health outcomes. Relevant existing literature was searched and assessed for suitability for inclusion in the review. Results were not consistent. However, it appeared that the balance leaned towards a detrimental effect of TFA intake and disease outcomes. The direction of relationship did not differ by gender, TFA assessment type, or study design. Future research is required to elucidate the effects of TFA from other dietary components on chronic health outcomes.

Funders of the project: Food Standards Australia New Zealand

Tackling overweight and obesity: Does the public health message match the science?

Investigators: 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

GROUP NAME

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.

Smoking and mental illness

Investigators: 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

Investigators: 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

Investigators: 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. (2014). Talking to kids about emotions matters more than you think. *The Conversation*. Retrieved from <https://theconversation.com/talking-to-kids-about-emotions-matters-more-than-you-think-21955>

GROUP NAME

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 Population 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.

Kulunga Aboriginal Research Development Unit

Aboriginal Consultative Committee Advising Research and Evaluation (ACCARE)

As part of the Institute's strategic planning process that was conducted in 2013, a parallel strategic process was undertaken to ensure that the needs of Aboriginal families were considered. This parallel process was led by Emerita Professor Rhonda Marriott (Senior Aboriginal Researcher), Dr Michael Wright (Senior Aboriginal Researcher) and Glenn Pearson (Manager Aboriginal Research Program) and supported by the Institute's Aboriginal Research Leadership Group.

The outcomes of these processes have led to the development of the Institute's Working Together Strategic Plan (2013 -2017) and the objectives of the Institute's Commitment to Aboriginal Children and Families (2013-2017) with a recommendation that ACCARE would be reconstituted as an advisory committee reporting directly to the Director Telethon Kids Institute – Professor Jonathan Carapetis.

With the exception of the Director the membership is now entirely comprised of Aboriginal people. These members have not been engaged to represent their regions rather that they bring from across the State a vast range and much

needed skills and experiences to assist in the Council's work.

The ACCARE members are:

- Kate George - Chair
- Rhonda Marriott
- June Oscar
- Josie Janz
- Ian Trust
- Darryl Kickett
- Jon Ford
- Jonathan Carapetis
- Glenn Pearson

The goal of ACCARE is:

To provide high level advice to the Director around strategic directions and operational elements relating to Aboriginal health research at the Telethon Institute with the aim of ensuring facilitation, translation and application of research finding into policy and practice.

Aboriginal Health Research Focus Area Steering Committee

As part of the Institute's Working Together Strategic Plan a Research Focus Area Strategic Framework was developed to reflect four key areas of research of which Aboriginal Health was one. Under each RFA a Steering Committee was established and comprised of 10-15 senior researchers drawn from across the Institute, PMH and SPACH.

The purpose of each RFA Steering

GROUP NAME

Committee is to facilitate the development and implementation of high quality collaborative research projects consistent with the Institute Strategic Plan and RFA research goals and to ensure our research makes a difference.

The Aboriginal Health RFA Steering Committee has acknowledged that it plays a dual role across the Institute in both promoting an increase in the numbers of Aboriginal health related research projects within the Aboriginal Health area as well as across the other three RFA's.

Over the last year the AHRFA Steering Committee has undertaken two Open Space Forums to create an opportunity for researchers to engage with the Aboriginal community. The outcomes of these forums will contribute to a deepening in the relationship between researchers and Aboriginal people to ensure that our research better reflects the needs of Aboriginal families as well as translates into positive change in the health and wellbeing of these families.

A third and final Open Space forum is planned in 2015 to look at identifying a process to prioritise our research.

Kulunga Aboriginal Research Development Unit (KARDU)

It is now one year since the launch of Working Together, the Telethon Kids Institute Commitment to Aboriginal Children and Families (2013-2018), which outlines a blueprint for action for the Institute to continue its work to use our research to answer the questions

that confront families in bringing up their children. The Institute established the KARDU to progress the key priorities outlined in the Commitment.

Aboriginal Governance

Ensuring a clear Aboriginal voice is heard and influences the Institutions work through an Aboriginal board member, the establishment of the Aboriginal Collaborative Council Advising Research (ACCARE) and the appointment of the Head, Aboriginal Research to the Institutes Leadership Team.

Setting Research Priorities

A key focus of KARDU is facilitating the involvement of Aboriginal families and communities in deciding what research best responds to their needs. Through the Aboriginal Health Research Focus Area two open forums were held with Institute researchers and Aboriginal community members and service providers to begin identifying what these research priorities are. A third will be held in the coming year.

Aboriginal Employment and Career Development Strategy

Through the Centre for Research Excellence in Aboriginal Health and Wellbeing the Institute has been developing the next generation of Aboriginal health researchers. In addition, KARDU has been developing an employment and career development strategy for the Institute for research, professional and other staff.

Research Development and Support

There are a number of research programs and projects at the Institute initiated to make a difference to the health and wellbeing of Aboriginal children and families and which in the future will come under the Aboriginal Health Research Focus Area. Some fall directly under KARDU, while others are managed under separate research groups and are discussed in more detail elsewhere and include:

- Alcohol and Pregnancy and Fetal Alcohol Spectrum Disorders Research Group
- Wesfarmers Centre for Vaccine and Infectious Disease
- Group A Streptococcus and Rheumatic Heart Disease Research Group
- Collaboration for Applied Research and Evaluation (CARE)

Additionally, KARDU has been actively working with researchers across the Institute to develop new programs of research that involve Aboriginal families and communities and in partnership with the Aboriginal Health Council of WA and the Rural Clinical School of WA to establish a research hub in Broome as the first site in creating the WA Aboriginal Health Knowledge Network.

Centre for Research Excellence in Aboriginal Health and Wellbeing

Our grant is a collaborative research venture between seven research

institutions and 10 Chief Investigators headed by Professor Fiona Stanley. The CEAHW brings the research strengths of each CI together in a cohesive program of community-based intervention research, well known both national and internationally, but with local relevance to Western Australia. It is being supported by the outstanding track record of the Institute working with government to inform policy and practice and build on past achievements by developing the next generation of Aboriginal health researchers and leadership among the CI team.

Highlights: The CEAHW funded 2 international visits. One by Emeritus Professor Michael Chandler from the University of British Columbia, Canada and the other by A/Prof Angela Bowen from the University of Saskatoon, Canada and Prof Sally Kendall from the University of Hertfordshire, UK.

The Australian Government funded a national Aboriginal and Torres Strait Islander Suicide Prevention Evaluation Project (ATSISPEP) led by Chief Investigator Prof Pat Dudgeon. A/Prof Roz Walker is responsible for overseeing the project implementation and outcomes.

The Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice was launched in Nedlands, June

Investigators: Prof Fiona Stanley, Prof Pat Dudgeon, Prof Dawn Bessarab, Prof Sandra Eades, Prof Rhonda Marriott, A/

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Prof Roz Walker, Dr Juli Coffin, Dr Cheryl Kickett-Tucker, Dr Michael Wright and Glenn Pearson.

Funding: NHMRC Centre of Research Excellence grant 2010 – 2015.

Looking Forward Project

Dr Michael Wright

The Looking Forward Project aims to change the way mental health services and drug and alcohol support services respond to the needs of Nyoongar families living in the southeast Perth metropolitan region (i.e. Armadale to Bentley). Mental illness and drug and alcohol concerns can be highly charged and emotive issues for the Nyoongar community living in this region. There have been significant challenges for the Project. In particular, the size and scope of serious and complex mental health issues impacting the Nyoongar community who have been involved in this Project.

Since the initial community consultation process undertaken in 2011 and 2012, the Project team, in conjunction with Nyoongar Elders, has facilitated a number of events and activities to assist service providers to develop an understanding of and respect for Nyoongar culture and its centrality to mental health and wellbeing. These activities include damper and bush medicine making, storytelling, community days and walks on country. These have helped prepare services to work more openly and authentically with Nyoongar Elders, as they seek to reflect on and reconfigure their

own service structures and delivery processes to better meet the mental health needs and drug and alcohol concerns of Nyoongar families.

Since late 2013 and throughout 2014, the Project team has facilitated meetings and activities with Nyoongar Elders and service providers to shape a way forward for systems change. During this time, the Project team collected data that would identify and describe the conditions necessary for respectful and authentic engagement between Nyoongar Elders and service providers. After some data analysis, an engagement process titled *Debakarn Koorliny Wangkiny* ('Steady Walking and Talking') was developed and trialed. Relationships are the foundation for this work and the two stakeholder groups have spent much time and effort building and deepening their relationships in order to be prepared for the next phase, that is, to co-design a culturally safe systems change innovation, shaped by this relationship-based approach.

The Elders are guiding service providers, who are engaged in a full multisensory experience, on a spiritual journey of transformation. Service providers are being introduced to many concepts that, for most, are totally unfamiliar to their worldview. For some it has been very challenging, but most are finding the experience enthralling, exciting and rewarding. The experience for most has been profound.

Project Funding: The project is funded by Lotterywest, Centre for Research

Excellence in Aboriginal Health and Wellbeing (Telethon Kids Institute, UWA), Curtin University, Mental Health Commission (WA), in partnership with Ruah Community Services (WA).

Getting our Story Right

Lead Investigator: Michael Wright, PhD, Research Fellow (Curtin University) and Chief Investigator (CREAHW)

A cross agency data linkage and analysis project to better understand and improve information about Aboriginal and Torres Strait Islander peoples using administrative data collections

Measures of the gap in living standards, life expectancy, education, health and employment between Indigenous and non-Indigenous Australians are primarily derived from administrative data sources. However, Indigenous identification in these data sources is affected by administrative practices, missing data, inconsistency, and error. Assessing whether the gap between Indigenous and non-Indigenous Australians has changed over time, based on data unadjusted for these sources of error can potentially lead to misguided conclusions. Combining administrative data on the same individuals collected from different sources provides a method by which a more consistent derived Indigenous status can be applied across all records for an individual within a linked data environment.

This project involved representatives from Telethon Kids Institute and UWA, the WA Data Linkage Unit at the Department of Health Western Australia, the Kurongkurl Katitjin Centre for Indigenous Australian Education and Research at Edith Cowan University, the Australian Primary Health Care Research Institute at the Australian National University, and the Australian Bureau of Statistics. In this project we used the Western Australian Data Linkage system to produce derived Indigenous statuses for individuals using a range of algorithms. We found that these algorithms reduced the amount of missing data and improved within-individual consistency.

In 2014 we published a paper on this project in the Australian Journal of Social Issues, outlining the findings of the project, and making recommendations for a method of combining data in the Western Australian Data Linkage System. These recommendations have been applied by the Western Australian Data Linkage Unit, and a 'best practice' Indigenous status has been made available to researchers as a variable which can be requested as part of any linked data project.

Investigators: Daniel Christensen (TKI), Geoff Davis (Data Linkage Unit, WA Department of Health), Glenn Draper (WA Department of Health), Francis Mitrou (TKI), Sybille McKeown (ABS), David Lawrence (TKI/ UWA), Daniel McAullay (Kurongkurl Katitjin Centre for Indigenous Australian Education and

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Research at Edith Cowan University, and Australian Primary Health Care Research Institute at the Australian National University), Glenn Pearson (TKI), Wavne Ridders (TKI), Stephen R. Zubrick (TKI/ UWA)

Funders: As a collaborative, cross-agency project, this project involved contributions from Telethon Kids (NHMRC Program Grant 572742), the Western Australian Department of Health, ABS, UWA, and ECU. The project was also part-funded by COAG through the National Indigenous Reform Agreement (Schedule F – Data quality improvements) to provide evidence supporting ‘National Best Practice Guidelines for Data Linkage Activities Relating to Aboriginal and Torres Strait Islander People’ (AIHW & ABS 2012).

Head of Group

Glenn Pearson

Staff and Students

A/ Professor Roz Walker – CREAHW - Telethon Kids Institute, Perth WA

Chrissie Easton – CREAHW - Telethon Kids Institute, Perth WA Research Co-ordinator

Dr Clair Scrine, PhD, - CREAHW - Telethon Kids Institute, Perth WA Senior Research Officer

Dr Carrington Shepherd, PhD - CREAHW - Telethon Kids Institute, Perth WA, Senior Research Officer

Charmaine Green – CREAHW

- Telethon Kids Institute, Geraldton, Research Assistant

Stuart Crowe - CREAHW - Curtin University, Research Assistant

Joy Neri - CREAHW - University of Western Australia, Research Assistant

Sue Renshaw - CREAHW - Pindi Pindi, Research Assistant

Margaret O’Connell M.Ed, B.A - Looking Forward Team, Telethon Kids Institute, Senior Research Officer

Rosemary Walley – Looking Forward Team, Research Assistant, B.ICD

Tanya Jones B.A (Psych) - Looking Forward Team, Telethon Kids Institute Project Officer

Kristen White MPA, MPH, LLB/BA – Program Manager, Aboriginal Health (Kimberley and Pilbara)

Honorary Appointments

Professor John Boulton - Emeritus Professor at the University of Newcastle, NSW;

Maureen Carter – CEO Nindilingarri Cultural Health Services in Fitzroy Crossing

Professor Pat Dudgeon – UWA School of Indigenous Studies

Dr Sandra Eades - Baker IDI Heart and Diabetes Institute

Dr Cheryl Kickett Tucker – Pindi Pindi Centre

Dr Daniel McAullay – Independent Research Consultant

Dr. Brian McCoy – University of Melbourne

Bridgette McNamara - Baker IDI Heart and Diabetes Institute

June Oscar – CEO Chief Executive Officer of Marninwarntikura Women’s Resource Centre in Fitzroy Crossing

Dr. Michael Wright – Curtin University

Students

Centre for Research Excellence in Aboriginal Health and Wellbeing:

Lina Gubhaju - Post-Doctoral Fellow, Baker IDI Heart and Diabetes Institute, Melbourne VIC. Assists Prof Eades.

Denise Groves - PhD student, Murdoch University

David Hendrickx - PhD student, UWA

Robyn Williams - PhD student, Curtin University, Perth

Ailsa Munns - PhD student, Curtin University, Perth WA

Clinton Schultz - PhD student, Griffith University, Qld

Jocelyn Kickett - Masters student, Murdoch University

Awards

Michael Wright – Curtin Indigenous Research Fellowship at Curtin University, February 2014

Fiona Stanley – Honorary doctorate at the Catholic University of Leuven in Belgium, February 2014

David Hendrickx – Stan Perron top up award

Carrington Shepherd –NHMRC Early Career Fellowship, June 2014

CI Rhonda Marriott – Lifetime Achievement Award for CATSINaM (Congress of Aboriginal and Torres Strait Islander Nurses and Midwives)

External Committees

National

- Prof Pat Dudgeon and Dr Juli Coffin, Prof Dawn Bessarab - National Indigenous Research and Knowledges Network (NIRAKN) –are members of this group.

- Prof Pat Dudgeon is co-chair of the Aboriginal and Torres Strait Islander Mental Health and Suicide Prevention Advisory Group (ATSIMHSPAG).

- Glenn Pearson - Indigenous HealthInfonet Advisory Board

- Glenn Pearson - Australian Bureau of Statistics (ABS) National Aboriginal and Torres Strait Islander Round Table

- Glenn Pearson and Roz Walker - National Aboriginal Disability Researcher’s Network.

Invited Presentations

A/Prof Roz Walker - 2nd National Conference in CQI in Aboriginal and Torres Strait Islander Primary Health Care (Lowitja). Melbourne 17 - 18 March

A/Prof Roz Walker - Congress Lowitja - Many mobs. One Vision. Creating a Healthy Future. Melbourne, 19 - 20 March

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Glenn Pearson - chaired a session at Congress Lowitja called Working Together: A different way of doing business. Melbourne, 19 – 20 March

A/Prof Roz Walker and Dr Clair Scrine presented on '50 years on : creating genuine research partnerships to improve Aboriginal Health'. AIATSIS Conference. Melbourne, 26 – 28 March

CI A/Prof Roz Walker and CI A/ Professor Dawn Bessarab - 'Breaking the Barriers: Transformative Research and Knowledge Translation to improve Aboriginal Health and Wellbeing. AIATSIS Conference

Prof Fiona Stanley - plenary talk - 'Clyde Herzman Memorial Lecture'. Vancouver, April

Prof Fiona Stanley - Population Monitoring as a Strategy for Improved Early Child Development: progress and new challenges. HELP (Human Early Learning Partnership). Vancouver, April

CI Prof Rhonda Marriott- PSANZ 18th Annual Congress 2014, Perth April

A/Professor Roz Walker and Prof Rhonda Marriott presented at the DOHaD conference, Perth, April

Dr Juli Coffin and Dr Cheryl Kickett-Tucker - Learning about Identity: An Australian Aboriginal perspective. WIPc:E, Oahu Hawaii, May

Prof Pat Dudgeon – Convenor Roundtable on Suicide Prevention, Perth, June

Prof Rhonda Marriott – Keynote speaker - Congress of Aboriginal and Torres

Strait Islander Nurses and Midwives CATSINaM, Scarborough, Perth September

Dr Michael Wright – facilitated a symposium – Working Together Makes Us Stronger. Perth August

Prof Rhonda Marriott – Cultural Security for Aboriginal women in urban settings - Health Care Forum, Aboriginal Maternity Services Support Unit. Perth, October

Prof Dawn Bessarab – Doing palliative care and being culturally safe and responsive in delivering services to Aboriginal people. WA Palliative Care Conference, Perth October

Prof Roz Walker – Community Co-researchers Training Workshop, National Empowerment Project, Perth November

Prof Pat Dudgeon – Back to the Future: Collective Reflexivities for Transformative Change. Perth November

Glenn Pearson – Identifying the Social, Cultural and Economic obstacles to Change - DoHAD Together Towards Tomorrow Conference -- Panel member Perth 9th April

Glenn Pearson – Aboriginal Research at the Telethon Kids Institute – Aboriginal Maternity Services Support Unit (AMSSU) Perth 10th June

Glenn Pearson – Aboriginal Research at the Telethon Kids Institute – SAHMRI Aboriginal Showcase Conference Adelaide 3rd August

Glenn Pearson – Panel member

Growing up Deadly and Strong
Workshop Lowitija Institute Melbourne
10th November

Looking Forward Project Team - AIATSIS
Conference, Canberra, 26th March

Looking Forward Project Team - District
Aboriginal Health Advisory Group
(Health Department), Fremantle, 2nd
April

Looking Forward Project Team -
National Drug Research Institute, Curtin
University, Shenton Park, Perth, 8th May

Looking Forward Project Team-
Presentation to Ombudsmans Office,
Albert Facey House, Perth, 22nd July

Looking Forward Project Team - Mental
Health Commission Co-Production
Forum Presentation, Curtin University,
29th July

Looking Forward Project Team - Dr
Michael Wright, Indigenous Forum,
The Mental Health Service (TheMHS)
Conference, Perth WA, 26th August

Looking Forward Project Team -
Symposium, The Mental Health
Services (The MHS) Conference, Perth,
28th August

Looking Forward Project Team -
Presentation to USA Eisenhower Fellow,
Cristal Thomas, Atlas Iron Pty Ltd, Perth,
9th September

Looking Forward Project Team -
Decolonisation workshop, School of
Social Work, Curtin University, 10th
November

ACTIVE research collaborations

Centre for Research Excellence in
Indigenous Ear Health, Professor
Amanda Leach, Menzies School of
Health Research

Centre for Research Excellence
in Improving Health Services for
Aboriginal and Torres Strait Islander
Children, Professor Karen Edmonds,
School of Paediatrics and Child Health,
University of Western Australia

Improving access to primary care for
Aboriginal babies in Western Australia:
The 'Stork' population based cluster
randomised trial, Professor Karen
Edmonds, School of Paediatrics and
Child Health, University of Western
Australia

ARC Discovery Indigenous Triple
PMP PCS Wrap Project, Professor
Rhonda Marriott, Aboriginal Health and
Wellbeing, Murdoch University

NHMRC Partnership Grant at the
Kulbaradi Aboriginal Centre, Murdoch

School of Social Work and Occupational
Therapy, Curtin University, Indigenising
the Social Work Curriculum

ACTIVE collaborations with industry

Aboriginal Health Council of WA

Rural Clinical School of WA

Ruah Community Services (Project
community partner)

Mental Health Commission WA

Western Australian Association for
Mental Health Services (WAAMHS)

Western Australian Drug and Alcohol
Network of Agencies (WANADA)

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Richmond Fellowship WA

Palmerston Association

North Metropolitan Health Service,
Youth Mental Health Services (Youth
Axis, YouthReach South)

Armadale Health Service, Mental Health
Services

Drug and Alcohol Withdrawal Network
(DAWN), St John of God Hospital
(Subiaco)

MercyCare

School of Social Work and Occupational
Therapy, Curtin University

Puntukurnu Aboriginal Medical Service

ACTIVE involvement with the community

The Aboriginal Health RFA held two open forums with Aboriginal community members to discuss working together and research priorities.

The Looking Forward Project have had ongoing communication with community organisations such as Langford Aboriginal Association and the Champion Centre (Armadale), along with local Aboriginal health services in the locations in which the project is being run (e.g. Kwinana).

Translation (any example of where the research has been used more broadly)

The Looking Forward Project team worked in partnership with the Elders' stakeholder group and some of the participating services to develop a Family and Community Day titled, Debakarn Koorliny Wangkiny ('Steady,

Walking and Talking'), as part of Mental Health Week (October) to develop greater awareness of the positive role of cultural identity and community and family support in the lives of those experiencing mental illness and drug and alcohol related issues. The event was in partnership with Richmond Fellowship WA, Champion Centre (City of Armadale), Ruah Community Services, Rotary Club, and WAAMH.

<http://mhw.waamh.org.au/assets/steady-walking-and-talking-together-mental-health-week.pdf>

The Looking Forward Project has been instrumental in bringing Nyoongar Elders and their families to work with the Institute to discuss shared health priorities relating to the Institute's Commitment to Working with Aboriginal Children and Families through a series of open space forums.

In late 2014, the Looking Forward Project team was approached by Curtin University's School of Social Work and Occupational Therapy to assist them with ways in which to develop their programs of teaching and learning to encompass Aboriginal ways of knowing, doing and being. The project team instigated a series of facilitated workshops with the Social Work teaching group, using the Debakarn Koorliny Wangkiny engagement framework to bring teaching staff together with local Elders to begin a conversation about the redevelopment of curriculum and teaching and learning practices. This work will continue into 2015 and occur at subject, program and

whole-of-School levels.

Health policies and guidelines directly influenced

Looking Forward meetings with the WA Mental Health Commission have informed policy discussions in relation to community based service settings and consumer engagement and participation (as demonstrated at the Mental Health Commission Co-Production Forum Presentation, Curtin University, 29th July)

The Handbook developed with Nyoongar Elders titled Open Hearts, Open Hands: A Spiritual Journey of Change (2013), is already being used in policy settings and is now available publicly via the HealthInfonet website: <http://www.healthinonet.ecu.edu.au/key-resources/promotion-resources?lid=28370>

Other achievements

In February of 2014, Dr Michael Wright took up the inaugural Indigenous Research Fellowship at Curtin University and presented about the Project to a staff gathering at the Centre for Aboriginal Studies.

Dr Wright and two Nyoongar Elders were interviewed by NITV for their segment, 'Noongar Danjoo', on the impact of suicide on Nyoongar families, in which Dr Wright and the Elders described the Looking Forward project and how it is changing the way services respond to the needs of families experiencing serious mental illness, grief and loss. The segment will be

aired in 2015.

The Institute unveiled and launched its monument commemorating that acknowledges that the Telethon Kids Institute is located on Nyoongar Whadjuk Boodjar in December

Looking at Language

Investigators: Professor Mabel Rice from the University of Kansas, Professor Cate Taylor and Winthrop Professor Stephen Zubrick from Telethon Kids Institute and Professor Shelley Smith from the University of Nebraska Medical Center.

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

GROUP NAME

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 children and families overall. The study has received 15-years continuous funding from the USA National Institutes (National Institute on Deafness and Other Communication Disorders). The project is a joint initiative between the Telethon Institute for Child Health Research and UWA and the USA's University of Kansas and University of Nebraska Medical Centre. All study participants and data collection is based in Western Australia.

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.

Funder of the project: National Institutes of Health (RO1DC05226, P30DC005803, P30HD002528)

Obesity

Investigating methods for managing childhood obesity

Investigator: Lisa Gibson (Telethon Kids)

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).

The Western Australian Pregnancy Cohort (Raine) Study

The Raine Study is one of the largest and most successful prospective cohorts of pregnancy, childhood, adolescence and now early adulthood to be carried out anywhere in the world. The cohort was established between 1989 and 1991 to determine how events during pregnancy and childhood influence health in later life with nearly 3,000 pregnant mothers joining the Raine Study. Follow up assessment of the families and their children were conducted at birth and then when the children were 1, 2, 3, 5, 8, 10, 13, 16, 18, 20 and 22 years of age. There are still over 2,000 of these children who are members of the Raine Study. The latest Raine Study assessment at age 22 was completed in June 2014. Over 1,000 participants came to the Centre for Sleep Science on UWA campus and did an overnight sleep study, asthma and allergy testing and various other assessments. This represents the biggest study of sleep in this age group in the world. In 2014 an audit of Raine Study Biological samples was completed by Dr Marion Macnish. The Raine Study has over 170,000 samples securely stored and catalogued across six sites.

During 2014, Raine Study researchers published 70 papers in peer reviewed journals. The Raine Study website has been improved and updated and information on Raine Study publications, research projects, resources and access to the Raine Study are available on the website www.rainestudy.org.au.

In 2014 NHMRC project grants

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were awarded to Professor Peter Eastwood to examine the prevalence, phenotype and genotype of common sleep disorders in the Raine Study parents and to Professor Pat Holt to examine the waxing and waning of asthma during transition from teens to adulthood in the Raine Study. An ARC grant was awarded to Professor Sharon Parker and Professor Leon Straker to examine work design and the dynamic interplay of work and person factors in the Raine Study. Funding support was awarded to Professor Eastwood and Professor Leon Straker from the Western Australia Department of Health (WADH) Future Health Initiative to audit and analyse biological samples in the Raine Study. Dr Gina Trapp and Dr Sarah Foster were awarded funding from the WADH Targeted Research Fund to examine alcohol outlet proximity and density and the implications for alcohol consumption patterns and mental health in adolescents and young adults.

Professor Ian Puddey retired from his position as Chairman of the Raine Study Executive Committee. He served as the inaugural Chairman of the Committee since 2005. Professor Puddey retired as the Dean of the University of Western of Australia, Faculty of Medicine, Dentistry and Health Sciences at the end of 2014. The position of Chairman of the Committee ceded to Professor John Challis

Professor George Yeoh represented the Raine Medical Research Foundation on the Raine Study Executive Committee

for over 10 years. Professor Yeoh has provided an enormous wealth of scientific knowledge and expertise to the Raine Study. He retired from this position in 2014. The Executive Committee welcomed Professor Paul Norman to represent the Foundation on the Executive Committee. Professor Susan Prescott accepted the Raine Study Executive Committee's invitation to join the Committee.

The Seventh Raine Study Annual Scientific Meeting was held on Friday 2 August 2013 at the UWA Club. The Event was opened by Peter Klinken. Over 100 Raine Study Researchers attended the meeting and participated in over 20 presentations.

After over 20 years of being located within the Telethon Kids Institute, the Raine Study moved to new premises at the University of Western Australia within the UWA School of Population Health in late 2014. The new address is 12-14 Parkway, Nedlands, UWA and these offices provide the Raine Study with increased capacity to perform assessments for future follow up studies.

Cohort Studies

Raine Study Anaesthesia

Investigators: Dr Britta Regli Von Ungern Sternberg, Dr Mary Hegarty, Professor Andrew Whitehouse

The Raine Cohort offers a unique opportunity to investigate the relationship between early exposure to surgery and anaesthesia, and

the possibility of developmental delay in childhood or adolescence. This research may also lead to the identification of the safest anaesthetic agents for use in infants and children. The benefits of investigating this relationship in the Raine Cohort are its prospective and longitudinal design, large and representative cohort, excellent retention rate and very detailed data collection.

Raine Study Asthma and Allergy

Investigators: Patrick Holt, Graham Hall, Peter Sly, Elysia Hollams, Anthony Bosco

Extensive research into the development of asthma and allergy has been conducted within the Raine Study and collaborating research groups. Ongoing projects include investigations into the molecular basis of asthma, the epidemiology through to genome wide association studies to unravel the genetic and environmental factors contributing to asthma and allergy. The Raine Study cohort participants have undergone extensive allergy and lung function testing at 5, 14 and 22 years of age.

2012-2014, NHMRC 1021858, G Hall, P Holt, E Hollams, Z Hantos. Transition from childhood to adult asthma: Predicting persistent and adult onset asthma in young adults in the Raine longitudinal birth cohort, \$984,248.

Raine Study Cardiometabolic

Investigators: Lawrie Beilin, Trevor Mori, Rae-Chi Huang, Sally Burrows, Wendy

Oddy

The cardio-metabolic group has been examining the effects of prenatal and postnatal factors, lifestyle and environmental factors on cardio-metabolic health during childhood, adolescence and adulthood. The group is examining childhood trajectories for adiposity, blood pressure and insulin resistance, and the association between parental and adolescent adiposity and cardio-metabolic risk.

2014 WA Telethon, Perth Children's Hospital Research Fund, RC Huang, E Davis, L Beilin, C Pennell, TPCHRF - Bedside to bench and back to paediatric obesity clinic: Enabling a powerful West Australian epigenetic resource, \$200,000.

2014-2016 NHMRC 1059655 RC Huang, K Lillycrop, G Burdge, J Craig, L Beilin, T Mori, W Oddy, K Godfrey, J Holbrook, Breaking the intergenerational cycle of obesity: a multigeneration population study of obesity epigenetics, \$1,086,101.

2012-2014, NHMRC 1037966, W Oddy, T Mori, L Adams, S Byrne, Nutritional determinants of cardiometabolic risk and mental health: from infancy to adulthood, \$481,725.

2012-2014, NHMRC 1030148, W Oddy, F Stanley, L Beilin, C Pennell, B Koletzko, Demmelmair, WG Peissner, Analysis of metabolic profiles in young adults from the Western Australian Pregnancy Cohort (Raine) Study by metabolomics: biomarkers for metabolic consequences of early programming by infant feeding type, \$323,250.

GROUP NAME

Raine Study Developmental Group

Investigators: Andrew Whitehouse, Murray Maybery, Jeffrey A Keelan

Each and every child develops in their own unique way. The 'Developmental research group' seeks to understand how and why children vary in the course of their cognitive, social and language development. The research group examines the links between genetic, biological and behavioural data. By understanding why children vary in their development, the research group aims to be able to identify children at risk of delayed development as early as possible, and devise therapies to help these children reach their full potential.

2011-2015 NHMRC 1003424, A Whitehouse, M Maybery, C Dissanayake, M Hickey, C Pennell, , Prenatal and early postnatal risk factors for autism spectrum disorders, \$671,938.

Raine Study Eating Disorders

Investigators: Karina Allen, Sue Byrne, Wendy Oddy

Eating disorders are highly complex and serious mental illnesses that occur most frequently in adolescents and young adults. Researchers in the Raine Study Eating Disorder research group are working towards the identification of factors that contribute to the development of these conditions. We are also identifying factors that may predict persisting eating difficulties once an eating disorder has developed.

2010 - 2014, NHMRC Early career research fellowship, K Allen, Eating disorders in Western Australia: Prevalence, maintaining factors, and prospective risk factors, \$288,000.

Raine Study Epigenetics

Investigators: Rae-Chi Huang, Craig Pennell, Lawrie Beilin, Trevor Mori, Sally Burrows, Jeffrey Craig (Murdoch Children Research Institute, Melbourne), Karen A Lillycrop, Graham C Burdge, Keith Godfrey (Southampton University)

The Raine Study Epigenetic research group is investigating the effects of epigenetic modification on adolescent body mass and markers of cardiometabolic health including cholesterol, insulin resistance and blood pressure. Obesity is a significant adult health problem, and is becoming increasingly common in children and adolescents.

2014-2016, NHMRC 1059711, RC Huang, K Lillycrop, G Burdge, J Craig, L Beilin, T Mori, W Oddy, K Godfrey, J Holbrook, The cycle of obesity, A two generation population study of obesity epigenetics, \$1,086,102.

Raine Study Growth

Investigators: Catherine Choong, Nooshi Rath, Julie Marsh, Helen Atkinson, Peter Sly

The Raine Study provides longitudinal measures of length, height and weight of individuals from birth to, currently, 22 years of age. The availability of genetic information from the Raine Study provided the opportunity for the Growth

Team to identify specific polymorphisms in the ghrelin gene that were associated with growth. Raine Study height data was also used to compare the Centres for Disease Control and Prevention (CDC) and World Health Organisation (WHO) reference/standards for height in children. The Raine Study also provide contemporary normative growth measures against which the RAINE Growth Group can assess growth in children affected by chronic diseases.

Raine Study Mental Health

Investigators: Monique Robinson, Andrew Whitehouse, Anne Smith, Jeff Cannon, Karina Allen, Vijay Panicker, Peter Jacoby, Craig Pennell

The Raine Study has collected detailed information on behavioural and emotional development and this information is used to understand the social and biological pathways that lead to mental health disorders. Information collected on mothers during their pregnancies has enabled the group to examine the relationships between the characteristics of prenatal life (e.g., exposure to chemicals, maternal stress, fetal growth) and mental health outcomes. Physical assessment and biological samples have been used to identify biological mechanisms that may influence mental health outcomes. The group has examined social and lifestyle factors that may contribute to mental health, including the family environment, schooling, friendships, sport, risk taking behaviour and bullying. Research has also been undertaken on diet and nutrition (including breast feeding)

and how this affects mental health outcomes.

Raine Study Musculoskeletal

Investigators: Leon Straker, Peter O'Sullivan, Anne Smith, Darren Beales

The musculoskeletal group is investigating the complex development of back and neck pain from childhood, through adolescence, into early adulthood, and the impact of backpain on work. Back pain is a leading contributor to work disability in the form of absenteeism (being away from work) and presenteeism (reduced productivity at work). Factors that contribute to the development of backpain in teenagers and young adults include physical factors (posture, fitness, motor competence, weight), lifestyle factors (computer and TV use, physical activity, diet, drug use), psychosocial factors (depression, anxiety, stress, coping, fear of movement, back pain beliefs), genetics (genes linked to stress response and pain thresholds) and other factors including sleep and chronic diseases such as asthma. The group is also examining the effects of sedentary behaviour (periods of inactivity for example working at a desk or watching television) health outcomes. During the 22 year follow up the group collected information on activity levels and work patterns to further research the links between work, activity and health outcomes.

2013-2014, SafeWork Australia, L Straker, D Beales, A Smith, R Moorin, G Pransky, P O'Sullivan, S Linton,

GROUP NAME

Work productivity loss associated with musculoskeletal pain in young adults, \$70,000.

2012-2014, NHMRC 1044840, L Straker, G Healy, M Tremblay, R Abbot, A Smith, G Mishra, A life course approach to characterising and predicting inactivity and sedentary behaviour of young adults, \$291,473.

Raine Study Nutrition

Investigators: Wendy Oddy, Georgina Trapp, Lucinda Black, Therese O'Sullivan, Gina Ambrosini, Siobhan Hickling, Wendy Chen She Ping-Delfos, Lawrie Beilin, Trevor Mori, Nick De Klerk, Monique Robinson

The Nutrition Group have investigated the dietary intake of the Raine Study cohort participants from birth through to 23 years of age. Information has been collected about breastfeeding, first foods and dietary intake through childhood, adolescence and early adulthood. Fasting blood samples were collected for biochemistry, metabolic and immunological biomarkers. The Group is a member of an international collaboration on 'Early Nutrition', a 36 institution, 12 million euro (AUS\$17.3 million) project. This collaboration is funded by an NHMRC European Union collaborative grant and aims to uncover the long term impact of early nutrition on later health.

2012-2014, NHMRC 1022134, WH Oddy, T Mori, L Adams, S Byrne, Nutritional determinants of cardiometabolic risk and mental health: from infancy to adulthood, \$481,725.

2012-2016, NHMRC 1037966, WH Oddy, F Stanley, L Beilin, C Pennell, B Koletzko, H Demmelmair, W Peissner, Analysis of metabolic profiles in young adults from the Western Australian Pregnancy Cohort (Raine) Study by Metabolomics: Biomarkers for metabolic consequences of programming by infant feeding type, \$323,250.

Raine Study Ophthalmology

Investigators: David Mackey, Alex Hewitt, Seyhan Yazar

The twenty year Raine Study follow up was conducted at the Lions Eye Institute and Sir Charles Gairdner Hospital by the Raine Study team, ophthalmologists, ophthalmology trainees, medical students, orthoptists, ophthalmic assistants and volunteers. This is one of the first studies to determine the prevalence and risk factors for eye disease in young adults, and to characterize ocular biometric parameters in a young adult cohort with myopia (short sightedness) being the most common condition. Data from the Raine Study combined with genetic information allows the group to participate in multinational research consortia investigating eye development, the basis of colour vision, and numerous eye disorders.

2012-2014, NHMRC 1021105, D Mackey, C Pennell, A Hewitt, T Young, C Hammond, M Coreneo, S Macgregor. Genome-wide association study (GWAS) for juvenile-onset myopia and its component measures to identify molecular pathways to prevent myopia,

\$482,445.

Raine Study Reproductive Health

Investigators: Roger Hart, John Newnham, Martha Hickey, Craig Pennell, Dorota Doherty, Jeffrey Keelan, Monique Robinson, Jennifer Marino

The Raine Study Reproductive Group is investigating the development and reproductive health in the Raine Cohort. Reproductive health is influenced by age, lifestyle (smoking, alcohol, nutrition), genetics, some medications and exposure to chemicals in the environment. The Group's research has focused on the age of puberty, menstruation in teenagers, Polycystic Ovarian Syndrome (PCOS), hormone exposure before birth, and male fertility. Members of this group are involved in the first long term study to analyse the long-term health outcomes of children born resulting from IVF treatment.

2013-2017, NHMRC 1042269, R Hart, C Pennell, D Doherty, M Robinson, The long-term consequences of IVF treatment for the offspring - a prospective cohort study using the Raine Cohort for comparison, \$1,552,096.

Raine Study Sleep

Investigators: Peter Eastwood, David Hillman, Nigel McArdle, Romola Bucks, Anne Smith, Elizabeth Davis, Rae-Chi Huang, Nicholas de Klerk, Craig Pennell, Eric Moses, Phillip Melton, Leon Straker, Stuart King

The Raine Study participants, at 22 years of age underwent a

comprehensive overnight laboratory-based sleep study at the UWA Centre for Sleep Science. The Sleep research group is utilising the unique longitudinal data collected on participants in the study to determine, for the first time, the prevalence, phenotype and risk factors for OSA and other sleep disorders in early adulthood. This study has generated an internationally unique dataset of full laboratory-based sleep studies in a group of young adults and represents the first Australian "longitudinal sleep cohort".

2012-2014 NHMRC1027449, P Eastwood, D Hillman, A Smith, N McArdle, R Huang, Childhood obesity and its relationship to adult sleep disordered breathing, \$843,060.

Head of Group

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Professor Leon Straker, Association Scientific Director

Jenny Mountain, MBA, MCLinEpi, Raine Study Program Manager

Angela Jacques MSc, Raine Study Biostatistician and Database Manager

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Jessica Tearne, PhD

Anett Nyaradi, PhD

Carly Herbison, PhD

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Seyan Yazar, PhD

Amelia Stephens, PhD

Elisha White, PhD

Esha Jamnadass, PhD

Anahita Hamidi, PhD

Robert Waller, PhD

James Slater, Masters

Naomi Heaps, Masters

Davinder Gill, Masters

Michelle Trevanan, Honours

Nicholas Lilleyman, Honours

Craig Hutchinson, Honours

Theses passed

Nicolle Warrington, PhD, UWA,
Modelling of complex longitudinal
phenotypes over childhood: Growth
trajectories in the developmental origins
of health and disease

Chi Le Ha, PhD, UWA, Studies of
antenatal and postnatal factors
predicting cardiovascular phenotypes
from birth to 17 years

Lauren Hollier, PhD, UWA, The
relationship between prenatal
androgens and early social
development.

Awards

Elisha White – Raine Study PhD top-up
Scholarship

Seyan Yazar – Raine Study PhD top-up
Scholarship

Carly Herbison – Raine Study PhD top-
up Scholarship

Denise Anderson – Raine Study Annual
Scientific Meeting Raine Medical
Foundation award for best presentation

Seyan Yazar - Raine Study Annual
Scientific Meeting Raine Medical
Foundation award for best presentation

Anett Nyaradi, UWA Graduate Research
School prize for Higher Degree by
Publication prize.

Rett Syndrome

International Rett syndrome study:

InterRett

Investigators: 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 Rettsyndrome.org (formerly 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 ~2,500 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 2014 we were awarded a further two years ongoing funding from Rettsyndrome.org to continue the management of the database. Our current aims are to:

1. To give families a strong voice in research about Rett syndrome,
2. To expand data collection to facilitate evidence-based management,
3. To focus on families who live in under-represented majority world countries, and
4. To further develop the InterRett infrastructure to enable linkage with other Rett syndrome and international rare disease database initiatives.

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.

GROUP NAME

Funders of the project:

Current: NHMRC Program Grant (572742), Rettsyndrome.org (2575), NHMRC Senior Research Fellowship Helen Leonard (572568).

Towards evidence based care for Rett syndrome: a research model to inform management of rare disorders

Investigators: 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 we asked clinicians to complete questionnaires relating to the characteristics of their patients for whom they requested MECP2 testing at one of the three Australian accredited laboratories. These are completed prior to the result of genetic testing being known. From mid-July 2011 to mid-July 2014 there were 276 referrals where a clinician could be contacted and agreed to participate. Questionnaires were completed and available for analysis on 243/276 (88.0%). Of the 243, 211(86.8%) were female and pathogenic MECP2 mutations were identified in 14.7% and in no males (12.8% positive overall). 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.

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 now been collected on 188 girls and women with scoliosis. 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 supplementing

the questionnaire data. We are also collecting video data and by year end 2014, 175 families had provided video footage of their daughter's functional abilities.

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 and the Children's Hospital, Adelaide.

During 2014 fourteen articles relating to Rett syndrome were published or accepted for publication by our group. These articles included investigations of scoliosis, poor growth, gastrointestinal dysmotility, gallbladder disease, bone health and communication in Rett syndrome. We have also investigated participation in activities in the community and have written a review on hand function in Rett syndrome.

Funders of the project:

GROUP NAME

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

Investigators: 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 dysmotility 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, NHMRC Program Grant (572742), NHMRC Senior Research Fellowship Helen Leonard (572568).

Publications 2014

1. Anderson A, Wong K, Jacoby P, Downs J, Leonard H. Twenty years of surveillance in Rett syndrome: what does this tell us? *Orphanet Journal of Rare Diseases*. 2014;9.
2. Andrews J, Leonard H, Hammond GC, Girdler S, Rajapaksa R, Bathgate K, Downs J. Community participation for girls and women living with Rett syndrome. *Disability and Rehabilitation*. 2014;36(11):894-9.
3. Baikie G, Ravikumara M, Downs J, Naseem N, Wong K, Percy A, Lane J, Weiss B, Ellaway C, Bathgate K, Leonard H. Gastrointestinal Dysmotility in Rett Syndrome. *Journal of Pediatric Gastroenterology and Nutrition*. 2014;58(2):237-44.

4. Downs J, Parkinson S, Ranelli S, Leonard H, Diener P, Lotan M. Perspectives on hand function in girls and women with Rett syndrome. *Developmental Neurorehabilitation*. 2014;17(3):210-7.
5. Downs J, Wong K, Ravikumara M, Ellaway C, Elliott EJ, Christodoulou J, Jacoby P, Leonard H. Experience of Gastrostomy Using a Quality Care Framework: The Example of Rett Syndrome. *Medicine*. 2014;93(28).
6. Freilinger M, Boehm M, Lanator I, Vergesslich-Rothschild K, Huber W-D, Anderson A, Wong K, Baikie G, Ravikumara M, Downs J, Leonard H. Prevalence, clinical investigation, and management of gallbladder disease in Rett syndrome. *Developmental Medicine and Child Neurology*. 2014;56(8):756-62.
7. Walker EM, Crawford F, Leonard H. Community participation: Conversations with parent-carers of young women with Rett syndrome. *Journal of Intellectual & Developmental Disability*. 2014;39(3):243-52.
8. Urbanowicz A, Leonard H, Girdler S, Ciccone N, Downs J. Parental perspectives on the communication abilities of their daughters with Rett syndrome. *Developmental Neurorehabilitation*. 2014. Epub 2014/02/26.

WA Register for Autism Spectrum Disorders

Emma Glasson, Keely Bebbington, Kavitha Dorairaj

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 long-term impact in areas of social interaction, communication and behaviour. The WA Autism Register is ongoing and since 1999 it has collected data on more than 4,500 individuals.

Funders of the project: Government of Western Australia, Department of Health.

Wesfarmers Centre of Vaccines and Infectious Diseases

The Wesfarmers Centre of Vaccines and Infectious Diseases was initiated in 2014 through funding received from Wesfarmers Limited. Infectious diseases are the number one killer of young children worldwide and the main reason for childhood hospitalisations in Australia. The Centre's mission is to reduce the burden of serious childhood infectious diseases by finding better prevention and treatment solutions. Reducing the burden of serious infections in Aboriginal children in Western Australia has our particular attention.

GROUP NAME

The Centre represents a number of independent researchers and research teams working on serious childhood infections primarily at the Telethon Kids Institute or elsewhere with clear existing links to the Institute. Research conducted under the umbrella of the Centre is focused on finding new solutions to improve the prevention and treatment of serious infections experienced by children or adolescents in WA and beyond. The breadth of research goes from bench to bed, including laboratory-based discovery and preclinical research, epidemiology and surveillance, clinical trials and implementation research.

The Centre aims to advance the research excellence and output of associated investigators, initiate novel high potential research ideas and attract and keep talented researchers through activities stimulating and facilitating new collaborations, connecting the bench and bed, facilitating community, partnerships and supporting training activities.

In 2014 research associated with the Centre's activities could be grouped into the following themes: Group A Streptococcal Diseases; Ear Health; Infectious Disease Epidemiology & Surveillance; Vaccine Clinical Research (the Vaccine Trials Group); and Implementation Research. For each theme, related research projects are summarized below.

All themes except that of Vaccine Clinical Research include studies that directly address Aboriginal child health.

In Australia, Group A Streptococcal disease now predominantly affects Aboriginal people. Middle ear infections occur in non-Aboriginal but more frequently and in a chronic form in Aboriginal children often leading to lifelong hearing loss. The epidemiological data-linkage studies use total population, mostly state wide data and include identifiers for Aboriginality, which makes it possible to assess and compare the burden of disease and risk factors for WA Aboriginal children and non-Aboriginal children separately. Studies that directly address finding solutions to improve the health of Aboriginal children have been marked (\$) at the beginning of the project title. This does not exclude that findings of other studies can be applied to advance the health of Aboriginal children.

Research Theme: Group A Streptococcal Diseases

The focus of the group is to understand and improve disease outcomes caused by the bacteria group A streptococcus (GAS). GAS causes a wide spectrum of diseases ranging from pharyngitis, skin sores to more severe forms of the disease including rheumatic fever (RF), rheumatic heart disease (RHD) and post-streptococcal glomerulonephritis (PSGN).

The group is headed by Prof. Jonathan Carapetis under whose leadership the group was awarded a Centre for Research Excellence in 2014. The END RHD CRE aims to develop an endgame for RHD in Australia. In 2014,

the group was assigned the lead site for CANVAS initiative, a trans-Tasman coalition to advance new vaccines for group A streptococcus. This is a first of its kind project aimed at fast tracking the development of anti-GAS vaccines. Another key highlight was the global partnership between Medtronic Philanthropy, RhEACH and the World Heart Federation to establish the RHD Action Alliance which will focus on reducing premature mortality from RHD by 25 percent by 2025 for those under 25 years of age, with an emphasis on developing comprehensive projects in targeted countries.

The END RHD CRE: Developing an end game for rheumatic heart disease in Australia

Investigators: Jonathan Carapetis, Nicholas de Klerk, Tom Snelling, Rosemary Wyber

Rheumatic heart disease (RHD) is caused by an abnormal immune reaction to some bacterial infections. Although RHD is rare in developed countries, Indigenous Australians still live with the burden of RHD. The END RHD CRE will explore risk factors for RHD, prevention with antibiotics, management of RHD and the potential for vaccine development. Individuals and communities experiencing RHD are integral partners to this work. The CRE will establish a strategy for ending RHD in Australia.

The END RHD CRE is a five year Centre of Research Excellence funded by the National Health and Medical Research

Council Australia in 2014. The END RHD CRE brings together 20 investigators from 16 institutions to develop an endgame for RHD in Australia. At the end of 5 years, the END RHD CRE will provide a stepwise roadmap to ending RHD in Australia and aim to produce a clear vision for achieving measurable disease control targets. The END RHD CRE will undertake a number of projects across several disciplines of research including epidemiology, biomedical sciences; implementation and translation; and understanding the RHD community with a special focus on documenting the experiences of those living with the disease.

Funding: National Health and Medical Research Council (NHMRC)

RHD Action Alliance

Investigators: RhEACH, World Heart Federation (WHF), Medtronic Philanthropy

In September 2014 RhEACH was named as a global partner in the largest private-sector contribution to date to address rheumatic heart disease (RHD). RHD is the most commonly acquired heart disease in children in many of the world's poorest countries. The RHD Action Alliance, funded by Medtronic Philanthropy is a consortium of global partners including RhEACH (headquartered at Telethon Kids Institute), Medtronic Philanthropy and the World Heart Foundation, and focuses on reducing premature mortality from RHD by 25 percent by 2025 for those under 25

GROUP NAME

years of age, with an emphasis on developing comprehensive projects in targeted countries. Over the next five years, funding at country levels will support efforts to integrate RHD interventions into primary care facilities, while leveraging current efforts focused on maternal and newborn care and HIV, including the training of community healthcare workers who will be the link between patients and the health system. All interventions will be implemented with the goal of strengthening the entire health system rather than supporting RHD-only projects. This partnership will work to influence policy decisions related to RHD, serve as a technical hub for RHD that can provide assistance to all countries where RHD is prevalent, advocate for people living with RHD and increase the network of supporters for RHD.

Announced in September 2014 this five-year, \$6 million (USD) Medtronic Philanthropy commitment will support a global movement to end premature mortality resulting from rheumatic fever and rheumatic heart disease. The World Heart Federation will serve as the Global Policy Partner, leading efforts to influence and inform policy decisions related to RHD. RHEACH will serve as a Global Technical Partner and scientific hub leading clinical and public health strategies to control RHD. Both organizations will provide policy and technical assistance to all countries where RHD is prevalent. Medtronic Philanthropy will lead the engagement of private sector in the RHD dialogue.

Funding: Medtronic Philanthropy

Coalition to advance new vaccines against group A streptococcus (CANVAS)

Investigators: Jonathan Carapetis, Meru Sheel

CANVAS is a Trans-Tasman initiative funded by the governments of Australia and New Zealand; aimed at accelerating the development of a vaccine for rheumatic fever prevention and reducing the burden of GAS associated diseases. The CANVAS program offers the opportunity to leverage public funds to take a vaccine through the initial stages of clinical development to the point of an efficacy study for GAS pharyngitis, in the expectation that this early stage “de-risking” will allow partners in industry and significant international organisations to enter the development program with confidence. CANVAS program incorporates an objective pre-clinical and clinical evaluation of leading GAS vaccine candidates currently in development. GAS is diverse with over 200 distinct strains identified to date. A successful vaccine must confer protection against the vast majority of GAS strains circulating in a target population, with different geographical regions having a different range of predominant strains. Furthermore, a GAS vaccine must not cause autoimmune cross reactivity with human tissue that is the hallmark of acute RF. In order to collectively address the hurdles associated with GAS vaccine development, three major

research focuses involve selection of minimal strain set that will represent a wide range of disease manifestations. Lead vaccine candidate will be selected on the basis of efficacy against the selected GAS strains. Finally, a health economic evaluation of interventions to control GAS infections to rationalize the investment in GAS vaccine development is also being undertaken.

Funding: National Health and Medical Research Council (NHMRC) and the Health Research Council (New Zealand)

Development of a longer acting formulation of Penicillin G for the treatment and prevention of acute rheumatic fever and rheumatic heart disease

Investigators: Jonathan Carapetis, Meru Sheel

ARF and RHD are rare in developed countries, prevalence and associated morbidity and mortality is high within developing countries. Most recent figures show the global prevalence of RHD to be as high as 34 million and number of deaths due to RHD to be greater than 345,000. In Australia and New Zealand, the disease burden amongst the indigenous communities is one of the highest in the world. The most effective recommended treatment of ARF requires four-weekly intramuscular injections of 1.2 million units of benzathine penicillin G (BPG). Secondary prophylaxis for ARF and RHD with BPG is recommended for a minimum of 10 years, and in some cases even for a life time. Adherence to

secondary prophylaxis is low and can be attributed to a combination of factors including, frequency and duration of injection, pain at injection site, access to health care providers (especially for those living in poor remote settings). This projects aims at developing a longer acting formulation of penicillin G, such that frequency of the injection can be increased up to 3-6 months. It is hoped that the total direct and indirect cost of the new formulation would be equal to or lesser than the annual cost of delivering current forms of secondary prophylaxis. The new formulation of penicillin will also aim at targeting the issues of poor quality of BPG available in developing countries.

Funding: Telethon - New Children's Hospital Research Fund

Genetic associations of rheumatic heart disease in Aboriginal Australian and Torres Strait Island communities

Investigators: Jonathan Carapetis, Jenefer Blackwell, Clancy Read

Although poorly understood, the pathogenesis of RHD appears to involve infections with "rheumatogenic" strains of Group A Streptococcus in a host with inherited susceptibility resulting in an abnormal immune response and the development of autoimmunity. This project aims to identify regions of the human genome that confer susceptibility to rheumatic heart disease (RHD) in Australian Aboriginal and Torres Strait Islander populations. Results may lead to improved diagnostics, therapeutics

GROUP NAME

and vaccines for RHD. The project will enroll approximately 500 remote Aboriginal people with RHD and 1,000 community-matched controls across the Northern Territory. A major component of this study is to explore better ways to undertake community consultation and gain informed consent for genetics research in Aboriginal people, and to develop appropriate mechanisms for governance of the use of data and samples in the long term. The study will be a model for the conduct of genetic studies in Aboriginal populations.

Funding: National Health and Medical Research Council (NHMRC)

Improving delivery of secondary prophylaxis for rheumatic heart disease

Investigators: Jonathan Carapetis, Clancy Read

Rheumatic heart disease (RHD) 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 (SP). Due to proven benefit and demonstrated cost effectiveness, secondary prevention of RHD remains the focus of most RHD control strategies. Secondary prophylaxis involves a four-weekly administration of penicillin for at least 10 years to all people with a history of ARF or RHD to control and reduce their chance of progressing to established, or more severe disease outcomes.

This study will evaluate whether an

intervention designed to optimize health systems improves the delivery of SP, using a stepped-wedge trial in 10 communities in the Northern Territory of Australia. A detailed mixed-methods evaluation will be undertaken to ascertain the degree to which adopting the systems-based intervention improves processes of RHD care and adherence to SP and which elements of the intervention are most effective in activating change. If successful, this model will provide a practical and transferable model for improving SP delivery.

Funding: National Health and Medical Research Council (NHMRC)

Ear Health

Otitis Media (OM) refers to disease of the middle ear. It is a common illness in young children, peaking in infancy and again in pre-school years. Otitis media is best described as a spectrum of disease, ranging from Acute OM (which may cause pain but in Aboriginal children is commonly asymptomatic) to Acute OM with perforation to Otitis Media with Effusion (OME, also known as 'glue ear') in which there is fluid present in the middle ear and fluctuating hearing loss, through to chronic suppurative otitis media (CSOM) when there is recurrent ear discharge through a perforated tympanic membrane associated with hearing loss. Otitis media can seriously affect speech, ability to learn language, childhood development, school performance and subsequent social and economic well-being.

In the general population, episodes of OM tend to resolve though a substantial number of children do require surgery. However, in Aboriginal children the disease starts within weeks of birth and chronic disease with hearing loss is common. The prevalence of CSOM is very high, up to 40% in some remote Aboriginal communities, well above the World Health Organization (WHO) threshold of 4% constituting “a public health emergency” requiring immediate attention.

Preventing Otitis Media to Give a Sound Start for School (Pina Palya Pina Kulilku, Good Ears Good Learning)

Investigators: Deborah Lehmann¹, Ruth Monck¹, Wenxing Sun¹, Lorraine Sholson¹, Fay Sambo¹, Kirsten Alpers¹, Tanyana Jackiewicz¹, Anne Mahony², Charles Douglas³, Michelle Forrest, Daniel McAullay⁴, Bega Garnbirringu Health Services, Ngunyntju Tjitji Pirni Inc, Francis Lannigan⁵, Sharon Weeks⁶, Bradley Gilchrist, Annette Stokes⁷, Christine Jeffries-Stokes⁷

1: Telethon Kids Institute; 2. WA Country Health Services, Goldfields; 3. Kalgoorlie-Boulder Population Health Unit; 4. Aboriginal Council of WA; 5. Princess Margaret Hospital for Children; 6. Professional Hearing Services, South Perth; 7. UWA Rural Clinical School of WA, Kalgoorlie

This project follows on from the Kalgoorlie Otitis Media Research Project, in which we found very high rates of otitis media (OM) and

associated hearing loss, high carriage of bacteria in the upper respiratory tract from a very young age in Aboriginal children, and an increased risk of OM among children exposed to environmental tobacco smoke. The overall aim is to have Aboriginal children hearing well by the time they start school.

The objectives of this project are to:

- (1) Develop and implement a multifaceted ear health promotion program in collaboration with Aboriginal organisations in the Goldfields.
- (2) Evaluate the impact and effectiveness of an ear health promotion program that includes (a) an awareness program, (b) training of 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

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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 ~30 times at community events and schools.

Interviews were conducted with members of the community at the start of the project and 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 was launched at a public event in Kalgoorlie in September 2014. Findings were presented at the 3rd OMOz Australian Otitis Media Conference in Melbourne in August 2014.

Project funding: Western Australian

Health Promotion Foundation
(Healthway)

WA Aboriginal Ear Health Project

Investigators: Peter Richmond^{1,2},
Deborah Lehmann¹, Victoria Stroud¹,
Karen Edmond^{1,2}

1. Telethon Kids Institute; 2. UWA
School of Pediatrics and Child Health

In collaboration with Karen Edmond, who heads the Centre of Research Excellence in Improving Health Services for Aboriginal And Torres Strait Islander Children (ISAC), and members of her team (Natalie Strobel and Kimberley McAuley) the Ear Health project has been conducting a mapping and gapping exercise to identify the gaps in knowledge in evidence regarding practices currently used to prevent and treat OM in Aboriginal children. The findings will help identify research priority areas to inform evidence-based policy.

To assist in identifying gaps in evidence and implementation of best practice, the Aboriginal Ear Health Project has also started to work on building partnerships to consolidate the various ear health activities across WA and gathering the various players involved in ear health from around the state. To support this there will be a Stakeholder Forum for people working in ear health across WA in March 2015. A steering committee to prepare for the Stakeholder Forum met in December 2014.

Members of the ear health steering committee included:

- Charles Watson, Curtin University and Health Department of WA (Chair)
- Melissa Vernon, WA Country Health Service (WACHS)
- Marianne Wood, Aboriginal Health Council of WA (AHCWA)
- Kathy Currie, Northern Territory Department of Health
- Professor Harvey Coates, ENT Surgeon, Princess Margaret Hospital for Children
- Belinda Bailey, Rural Health West
- Deborah Lehmann, Telethon Kids Institute
- Menzies School of Health Research
- Francis Lannigan, ENT Surgeon, Princess Margaret Hospital for Children
- Peter Morris, Menzies School of Health Research and Royal Darwin Hospital
- Karen Edmond, School of Paediatrics and Child Health, University of Western Australia
- Hasantha Gunasekera, University of Sydney
- Peter Richmond, School of Paediatrics and Child Health, University of Western Australia
- and Paediatrician & Paediatric Immunologist, Princess Margaret Hospital for Children

- Ms Helen Humes, Centre Care
- Ms Victoria Stroud, Telethon Kids Institute

The Ear Health project is being done in the context of a national collaboration around ear health research and advocacy that will be coordinated through the recently awarded NHMRC Centre of Research Excellence in Indigenous Ear health.

Dissolving the glue in glue ear: assessment of the use of Dornase alfa as an adjunct therapy to ventilation tube insertion.

Investigators: Peter Richmond^{1,2}, Ruth Thornton^{1,2}, Stephanie Jeffares (study coordinator)¹, Harvey Coates², Shyan Vijayasekaran², Peter Jacoby¹, Lea-Ann Kirkham^{1,2}, Paul Bumbak³

¹Telethon Kids Institute; ² UWA School of Paediatrics and Child Health; ³. St John of God Health Care, Perth

We have demonstrated that the presence of bacteria in biofilm within the middle ear contributes to the persistence and recurrence of ear infections. We have also shown that these biofilms can stay in the ears in big nets of DNA that are produced by the children's own immune responses.

This is a double-blinded phase IIB trial studying the safety, tolerability and efficacy of the off-licence use of Dornase alfa (an agent to cut up the extra DNA) in reducing future ventilation tube insertions in children with chronic otitis media effusion and recurrent acute otitis media.

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To be eligible for this study the child must be between 6 months and 5 years of age; undergoing surgery for ventilation tube insertion for recurrent acute otitis media and/or otitis media effusion for the first time; and have had bilateral fluid for 3 months or longer. A child will have the investigational treatment (Dornase alfa) administered in one ear and the same volume of 0.9% sodium chloride (salty water) administered to the alternate ear at the time of surgery.

The recruitment target of 60 children was achieved in April 2014 and a total of 20 participants have completed all study visits while 40 remain to present for the last two follow-up visits.

Funding

State Health Research Advisory Council Grant, Princess Margaret Hospital for Children Translational Research Grant.

Dynamics of Haemophilus haemolyticus and nontypeable Haemophilus influenzae colonisation in otitis-prone children

Investigators: Lea-Ann Kirkham^{1,2}, Selma Wiertsema^{1,2}, Peter Richmond^{1,2}, Deborah Lehmann¹, Tom Riley³, Amanda Leach⁴, Heidi Smith-Vaughan⁴ and Peter Jacoby¹

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. PathWest/UWA School of Pathology and Laboratory Medicine; 4. Menzies School of Health Research, Darwin

Summary

Approximately 2 million children suffer from otitis media (middle ear infection, OM) in Australia each year. The health, social and financial costs of OM to Australia are substantial, with treatment alone estimated to cost \$100-400 million/year. In Australia, the bacterium nontypeable Haemophilus influenzae (NTHi) is the predominant cause of OM. A pneumococcal conjugate vaccine (Synflorix[®]) that includes an NTHi protein D carrier has been licensed in Australia, which has the potential to reduce the burden of OM through inducing protein-D specific immune responses. Accurate surveillance of the impact of this vaccine is hampered by another bacterium, H. haemolyticus (Hh), which masquerades as NTHi and cannot be distinguished using standard techniques. This has resulted in inaccurate surveillance. We are developing sensitive and specific molecular assays to accurately identify NTHi and Hh. These assays will be important for studies assessing the impact of Synflorix vaccination and other new OM-targeted vaccines.

Funding: NHMRC (2011-2014)

Evaluation of Haemophilus haemolyticus as a preventative therapy for ear disease

Chief Investigators: Lea-Ann Kirkham^{1,2}, Ruth Thornton^{1,2}, Peter Richmond^{1,2}, Peter Hermans³

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. University of Nijmegen, the Netherlands

Colonisation of the respiratory tract with nontypeable *Haemophilus influenzae* (NTHi) is essential for development of infection. We have found that children at risk of developing NTHi otitis media are less likely to be colonised with a related harmless bacterium called *Haemophilus haemolyticus*. We have also shown in-vitro that pre-treatment of human respiratory epithelial cells with *H. haemolyticus* can protect the cells from being infected with NTHi. We believe that *H. haemolyticus* could be used as a probiotic to prevent NTHi colonisation of the respiratory tract, which in turn may prevent development of otitis media. This study will provide in-vivo proof of principle whether treatment of the respiratory tract of mice with *H. haemolyticus* can prevent NTHi otitis media. We will also develop fluorescent probes for microscopy to examine how *H. haemolyticus* interacts with NTHi and with respiratory cells to determine how *H. haemolyticus* prevents NTHi colonisation, and guide its use as a preventative therapy for otitis media in children. Successful completion of this study will allow more significant investment through research commercialisation or NHMRC development funding.

As NTHi colonisation and otitis media occurs so early in life, particularly in Indigenous children, preventative therapies need to provide early protection. This could be in the form of a probiotic *H. haemolyticus* nasal spray, either directly administered to neonates, infants or even given to expectant mothers to promote

colonisation of their babies with a harmless commensal rather than NTHi. In older otitis-prone children, a nasal probiotic spray following antibiotic use could ensure that nasopharyngeal commensals rather than pathogens re-colonise the respiratory tract, thereby reducing the likelihood of recurrent infection.

Funding: Telethon-Perth Children's Hospital Research Fund 2013

Infectious Diseases Epidemiology & Surveillance

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

Investigators: Hannah Moore¹, Nicholas de Klerk¹, Peter Jacoby¹, Denise Anderson¹, Alexandra Hogan², Kathryn Glass²

1. Telethon Kids Institute; 2. Australian National University, Canberra

Acute lower respiratory infections, or chest infections, such as bronchiolitis, influenza, pneumonia and whooping cough are a major cause of morbidity in children. This project follows on from previous work of the infectious disease epidemiology research group to investigate the pathogen-specific burden of respiratory infections, and focuses on bronchiolitis caused by respiratory syncytial virus (RSV). Using a linked dataset of RSV detections in children from 2000 to 2005, the aim of

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the study is to develop a mathematical model of virus transmission dynamics describing the flow of individuals in a population from a pre-infectious (susceptible) state, to an infectious state and then recovered or immune state. Based on such a model it is possible to characterise and accurately mimic seasonal epidemics of respiratory syncytial virus to predict the impact of different intervention strategies on disease burden.

In collaboration with researchers at the National Centre for Epidemiology and Population Health at the Australian National University (Canberra), we have developed a base model for RSV that accurately mimics the viral activity in children aged < 2 years in metropolitan Western Australia: this was published in 2014. This model can now be extended to other geographical areas of Western Australia. We are also in the process of understanding the climatic drivers of RSV infections across different climate areas of Western Australia by identifying associations with specific weather variables such as minimum and maximum temperature and relative humidity. Data analysis has progressed in 2014 and we anticipate publishing first results in 2015.

Project funding: NHMRC Early Career Fellowship (HM) 1034254

Identifying opportunities for preventing respiratory infections in children through integrating population-based health and laboratory data (Triple I project)

Investigators: Hannah Moore 1, Christopher Blyth 1,2, Peter Jacoby 1, Faye Janice Lim 1, Parveen Fathima 1, Tasnim Abdalla 1, Nicholas de Klerk 1, Deborah Lehmann 1, Kim Carter 1, David Hendrickx1, Alexandra Hogan 3, Kathryn Glass 3

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. Australian National University, Canberra

This project investigates the epidemiology of acute lower respiratory infections in young children. The pathogens that most commonly cause acute lower respiratory infections in children include respiratory syncytial viruses, influenza viruses, parainfluenza viruses, rhinoviruses, adenoviruses, *Streptococcus pneumoniae* and *Bordetella pertussis*. Often separate pathogens can be found simultaneously in children with respiratory infections (known as co-infection) and there is mixed evidence to suggest that co-infection results in worse clinical outcomes than single infection. This project will use data linkage to identify the contribution of different pathogens in causing acute lower respiratory infections resulting in children being hospitalised or presenting to the emergency department between 1996 and 2012 in Western Australian. The specific aims of this project are: 1) to quantify the pathogen-specific burden of acute lower respiratory infections in Western Australia 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 respiratory infection outcomes and document the relative contribution of individual respiratory pathogens to these outcomes; and 3) to evaluate the direct and indirect population impact of paediatric immunisations on hospitalisations and emergency department presentations for acute lower respiratory infections, their related conditions (such as febrile convulsions) or other vaccine-preventable infections by conducting pre- and post-vaccination introduction temporal trend analyses.

The de-identified linked data for this project were received in 2014 and data cleaning and developing analysis plans were the focus of this year. To inform the analysis plan, we established a Triple I Scientific Steering Committee consisting of all the named investigators and other key stakeholders with an interest in acute lower respiratory infections. In 2014, we convened two meetings of the Scientific Steering Committee. Data cleaning and analyses will continue in 2015 and we anticipate that we will present results from first analyses in 2015.

Project funding: NHMRC New Investigator Project Grant

Linkage of the Australian Childhood Immunisation Register (ACIR) and state-based registers to evaluate and inform Australia's immunisation program

Investigators: Hannah Moore¹, Christopher Blyth^{1,2}, Nicholas de Klerk¹,

Peter Richmond^{1,2}, Parveen Fathima¹, Tom Snelling¹, Heather Gidding³, Bette Liu³, Peter McIntyre³, Louisa Jorm³

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. University of New South Wales, Sydney

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, children living in remote areas, and children 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, are required. Currently, this information is derived from stand-alone databases such as the Commonwealth funded- Australian Childhood Immunisation Register and compared to separate state-based databases of disease notifications or hospitalisations. While studying these datasets in isolation can be informative, their linkage would allow far more accurate analysis on the relationship between vaccination uptake, timeliness of vaccination, and development of disease in various population sub-groups.

Through collaborations with

researchers in New South Wales, we developed a cross-jurisdictional project linking data on administrative databases for children born in NSW and WA from 2000 to 2012, including data on births and deaths, immunisation records, hospitalisation admissions, emergency department visits, and infectious disease notifications (e.g. whooping cough, pneumococcal disease and influenza). The linked data will allow identifying characteristics of children who are not receiving vaccinations on time; calculate the effectiveness of vaccinations in preventing disease; and comparing the effectiveness of vaccinations between different risk groups, over time, and between NSW and WA.

In 2014, the Public Interest Certificate authorising the release of ACIR data to the Data linkage unit at AIHW was issued and all other approvals from the relevant data linkage units, ethics committees and data custodians were obtained. The linked data was made available through a remote data access laboratory, known as the Secure Unified Research Environment (SURE) in February 2015. Data cleaning and analysis will be the focus of this project over the next few years.

Project funding: Population Health Research Network Proof of Concept Collaboration #4. The Population Health Research Network is a capability of the Australian Government National Collaborative Research Infrastructure Strategy and Education Investment Fund Super Science Initiative

NHMRC Project Grant APP1082342

The pathogen-specific burden of hospitalisation for enteric and blood stream infection in children and young people in Western Australia

Investigators: Hannah Moore¹, Tom Snelling¹, Claire Waddington¹, Christopher Blyth^{1,2}, Thomas Riley³, Deborah Lehmann¹, Parveen Fathima¹

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. UWA Microbiology and Immunology

Enteric or gut infections cause significant mortality and morbidity in both resource rich and poor settings. In Western Australia, enteric infections are one of the leading causes for infection-related hospitalisations in children under the age of 2 years. Aboriginal infants are 8 times more likely to be admitted for enteric infections than non-Aboriginal infants.

Although an enteric infection is usually self-limiting, it can lead to acute morbidity through dehydration, and chronic morbidity in cases of under-nutrition. Furthermore, certain enteric pathogens can translocate into the normally sterile bloodstream causing bloodstream infection and sepsis. The pathogens causing enteric infection are geographically, seasonally and temporally variable. Rotavirus has been the single most important cause of enteric disease in Western Australia, the rest of Australia and globally, while infections due to the bacteria *Campylobacter* spp., *Salmonella* spp., *Shigella* spp. or parasites are

also frequently reported in infants living in the Northern Territory, and children < 5 years in remote Western Australia, especially Aboriginal infants. Routine rotavirus vaccination commenced in mid-2007 and since then hospitalisations due to rotavirus-specific and all-cause gastroenteritis have declined. We hypothesise that rotavirus immunisation has not only had a direct impact on preventing rotavirus gastroenteritis, but also has an indirect effect on preventing disease caused by other enteric pathogens by reducing their transmission.

Because of our capacity to directly link hospitalisation records with pathogen-specific pathology data, we are in a unique position to address this hypothesis in Western Australia. We will determine the pathogen-specific burden of community-acquired enteric and bloodstream infections in Aboriginal and non-Aboriginal children presenting to the emergency department or being hospitalised across the state of Western Australia, and will investigate temporal and seasonal trends of enteric pathogens, risk factors for hospitalisations and assess the impact of co-morbidities on disease outcome. This study will provide novel understanding of the overall impact of the rotavirus vaccination program, especially among Aboriginal children, and will inform future preventive and management strategies.

In 2014, ethical approvals and data custodian approvals were obtained

from all relevant ethics bodies and custodians in Western Australia. We anticipate that the linked data will be received by the project team in 2015.

Project funding: Princess Margaret Hospital Foundation New Investigator Project Grant 2013

Evaluating the use and effectiveness of passive immunisation in reducing RSV-associated morbidity in high risk infants

Investigators: Hannah Moore¹, Tasnim Abdalla¹, Tom Snelling¹, Tobias Strunk², Anthony Keil³, Nicholas De Klerk¹, Peter Richmond²

1. Telethon Kids Institute; UWA School of Paediatrics and Child Health; 3. PathWest Laboratory Medicine & Department of Microbiology, Princess Margaret Hospital

Respiratory syncytial virus (RSV) is one of the main causes of acute lower respiratory infections in young children. Clinical risk factors such as prematurity, chronic lung conditions or congenital heart disease increase the susceptibility of infants to RSV infections. In Australia the strategy to prevent serious RSV disease in high-risk infants is through the use of an expensive monoclonal anti-RSV antibody, palivizumab. Palivizumab is given as monthly injections during the RSV peak season, usually from May to October. However, there is no uniform national guideline or policy on the use of palivizumab in Australia. Few studies conducted in other countries have shown that a compliant use of monthly injections of

palivizumab can reduce RSV infections and associated hospitalisations. In Australia there has never been an evaluation of the efficacy of palivizumab in preventing RSV disease. This data linkage cohort study aims to evaluate the use and compliance with palivizumab and its effectiveness in preventing RSV infections. The cost-effectiveness of palivizumab will also be analysed. We will link data stored in the Neonatal Clinical Care Unit Database (NeoBase), Midwives Notification System, Princess Margaret Hospital and King Edward Memorial Hospital Dispensary Databases, Death Register, Hospital Morbidity Database System, Emergency Department Data Collection, and the PathWest Laboratory Database. The NeoBase will be used to identify high risk infants born between 1st January 2002 and 31st December 2013 and admitted to Level 3 Neonatal Intensive Care Unit at KEMH and PMH.

Funding for this project was received mid-2014 and the application for linked data was submitted at the end of 2014. All project approvals are anticipated to be obtained in 2015 with receipt of the linked data anticipated to be late 2015.

Project funding: Telethon-Perth Children's Hospital Research Fund Grant 2013

Validating and enhancing population-based data linkage for infectious disease research

Investigators: Hannah Moore¹, Christopher Blyth^{1,2}, Janice Lim¹

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health

Acute lower respiratory infections are a major cause of childhood morbidity, with higher rates of infection in Aboriginal children. It is a recommendation that children hospitalised with respiratory infections have a laboratory investigation to determine the causative pathogen. This is essential to guide patient clinical management 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 Western Australia linked to a laboratory record from 2000-2005. Linkage was particularly low in non-metropolitan areas: <5% in some remote areas and <10% in rural areas. Given the low levels of laboratory data linkage across the State, we set out to determine whether hospitalised children are either being under-investigated for respiratory pathogens or if there are deficiencies within our data linkage extraction protocols. We developed a medical chart review that was conducted in 7 hospitals across Western Australia. The primary purpose was to document the proportion of ICD10-coded respiratory infection hospitalisations that had any microbiological investigations.

Chart reviews were completed for 746 hospital admissions in children aged less than 5 years, who were admitted to hospital with a chest infection between 2000 and 2011. We reviewed admissions from Princess Margaret

Hospital for Children, Joondalup Health Campus, Fremantle Hospital, Bunbury Regional Hospital, Geraldton Hospital, Broome Hospital and Derby Hospital. These hospitals were chosen because they represented >55% of hospital admissions for chest infections in children in Western Australia. We compared the proportion of admission records with evidence of a laboratory test to the proportion of children recorded as having laboratory tests through our previous data linkage work. We also determined the differences in requests for laboratory tests in different areas, Aboriginal and non-Aboriginal populations and two time periods (2000-2005 and 2006-2011).

From 746 records, 571 (77%) had a laboratory investigation requested or performed compared to 46% in our population-based data linkage study. Laboratory investigations were reported more frequently in 2006-2011 compared to 2000-2005, particularly among infants aged 6-11 months, Aboriginal children and children admitted to rural or remote hospitals, although this increase was not uniformly distributed among all hospitals. We found that very young infants (aged <6 months) and children admitted to metropolitan hospitals were most likely to have a laboratory investigation. A manuscript describing these findings is currently under review.

Project funding: Telethon Institute for Child Health Research Small Grant 2012-2013

Monitoring carriage of Streptococcus

pneumoniae among Aboriginal children and adults in Western Australia

Investigators: Anke Hoskins¹, Tom Snelling¹, Deborah Lehmann¹, Deirdre Collins¹, Janice Lim¹, Kalpani Senasinghe¹, Peter Richmond^{1,2}, Jacinta Bowman³, Natalie Thomsen³, Tom Riley³, Carolien Giele⁴, Paul Effler⁴, Amanda Leach⁵

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. UWA Microbiology and Immunology; 4. WA Department of Health; 5. Menzies School of Health Research

Streptococcus pneumoniae is a bacterium that can cause invasive pneumococcal disease (IPD) including meningitis, pneumonia and septicaemia (blood poisoning). It is also a cause of middle ear infections. 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 has been introduced to the immunization schedule for Aboriginal children in 2001 and was replaced in July 2011 with Prevenar-13™, which covers six additional serotypes. A pneumococcal polysaccharide vaccine (Pneumovax™) covering 23 serotypes is offered to adults.

Pneumococci are carried in the back of the nose of healthy as well as sick

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individuals and the acquisition of pneumococci is prerequisite to develop disease. Surveillance of pneumococcal carriage offers complementary information to data on IPD on serotypes circulating in the population. This study aims to monitor the impact 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.

Due to limited funds, data collection from remote communities of WA was restricted. Pernal swabs and ear swabs were collected from participants attending metropolitan Aboriginal clinics and from one rural community (Katanning). To date we have collected 2850 pernasal swabs and 53 swabs of middle ear discharges. Pneumococcal carriage rates dropped slightly after the introduction of Prevenar-13™ but remain high in young children 6 – 23 months of age (70-80%). More than 60% of children < 6 months of age carried pneumococci. Since 2008, 45 different pneumococcal serotypes have been 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. Carriage of 19F remains common despite its inclusion in the pneumococcal vaccines. A manuscript with the title “Effect of 13 valent pneumococcal

conjugate vaccine and predictors of pneumococcal carriage in the Western Australian Aboriginal population” is in preparation.

Funding: Collaboration for Applied Research and Evaluation (CARE), Western Australian Department of Health

NHMRC Project Grant #545232 (in 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

Investigators: Deborah Lehmann¹, Janice Lim¹, Hannah Moore¹, Catherine Harrison¹, Judith Willis¹, Aoiffe McLoughlin¹, Carolien Giele² and Anthony Keil³

1. Telethon Kids Institute; 2. WA Department of Health; 3. PathWest Laboratory Medicine & Department of Microbiology, Princess Margaret Hospital

This project involved the analysis of the Invasive Pneumococcal Disease (IPD) surveillance data collected by the Vaccine Impact Surveillance Network (VISN) between 1997 and 2007 to investigate the underlying co-morbidities and risk factors associated with IPD.

Major findings are:

- Approximately 65% of IPD cases occurred in adults aged ≥15 years
- Pneumonia was the most

common diagnosis: 61% of non-Aboriginal and 49% of Aboriginal adult IPD cases

- Cardiovascular disease and chronic respiratory disease were the most common co-morbidities in non-Aboriginal adults ≥15 years
- Smoking and excessive alcohol uses were the most common risk factors in Aboriginal adults ≥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

The findings of this study have been published in 2014 in the *Pneumonia journal* (vol. 4, p 24-34).

Funding: 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)

Investigators: Christopher Blyth^{1,2}, Deborah Lehmann², Paul Effler³, Peter Richmond^{1,2}, Anke Hoskins², Kalapani Senasinghe²

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. WA Department of Health

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 pneumoniae 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

Funding: WA Department of Health

West Australian Influenza Vaccine Effectiveness Study (WAIVE)

Investigators: Christopher Blyth^{1,2}, Peter Richmond^{1,2}, Chris Robbins (study coordinator)², Paul Effler³, David

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*Smith*⁴, *Heath Kelly*⁵, *Gabrielle Willis*², *Peter Jacoby*², *Hannah Moore*², *Avram Levy*⁵, *Meredith Borland*⁶, *Jennifer Kent*², *Katie Lindsay*³ and *Anthony Keil*⁷

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. WA Department of Health; 3. PathWest Laboratory Medicine; 4. Royal Melbourne Hospital; 5. UWA School of Pathology and Laboratory Medicine; 6. Princess Margaret Hospital; 7. PathWest Laboratory Medicine & Department of Microbiology, Princess Margaret Hospital

This prospective observational study is designed to evaluate the effectiveness of trivalent influenza vaccine (TIV) in young children and to assess the burden of influenza in young children and their families. Children aged between 6 months and 5 years presenting to Princess Margaret Hospital for Children (PMH) Emergency Department or admitted to a hospital ward with an influenza-like-illness (ILI) are eligible for enrolment.

In 2014, the 7th consecutive year that the study has run at PMH, we enrolled 548 children between early July and mid-October. 22% of the children enrolled tested positive for influenza. Parents completed two questionnaires details about the child's illness and its impact on the child and the family, attitudes to influenza vaccine, and details about influenza-like illness in other household members at the same time.

With data collected over the previous six influenza seasons (2008, 2010-

2014), the WAIVE study has been able to demonstrate that the overall vaccine effectiveness of TIV is 70% in preventing medically attended laboratory proven influenza in children. This is comparable to the effectiveness in young adults. It also has demonstrated that TIV is effective in children less than 2 years of age. Despite demonstrated vaccine effectiveness, vaccine uptake is still low.

Influenza vaccination is recommended for all children in Western Australia age 6 months to 5 years. To date, there has been little evidence demonstrating that influenza vaccination prevents influenza in very young children. The data from this study demonstrate that the influenza vaccination prevents 2 out of 3 children from presenting to hospital with influenza.

Project funding: WA Department of Health

FLuCAN - A Rapid Alert System for Severe Respiratory Illness (The FluCAN Surveillance system)

Investigators: Christopher Blyth^{1,2}, *Carolyn Finucane* (study coordinator)², *Allen Cheng*³, *Paul Kelly*⁵, *Tom Kotsimbo*⁵, *Heath Kelly*⁶, *Tony Korman*⁵, *Deb Friedman*⁶, *Louis Irving*⁷, *Sanjaya Senanayake*⁸, *Grant Waterer*⁹, *Simon Brown*¹⁰, *Mark Holmes*¹¹, *Cameron Hunter*¹², *Simon Bowler*¹³, *John Upham*¹⁴, *Graham Simpson*¹⁵, *Stephen Brady*¹⁶, *Saliya Hewagama*¹⁷, *Dominic Dwyer*¹⁸, *Kristine Macartney*¹⁷, *Peter Wark*¹⁸

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. Monash University, Melbourne; 4. ACT Health Directorate, Canberra; 5. Monash Medical Centre, Melbourne; 6. Barwon Health, Melbourne; 7. Royal Melbourne Hospital, Melbourne; 8. Australian National University, Canberra 9. UWA School of Medicine and Pharmacology, Royal Perth Hospital Unit; 10. UWA Centre for Medical Research; 11. University of Adelaide, Adelaide; 12. Royal Hobart Hospital, Hobart, Tasmania; 13. Mater Hospitals, Brisbane; 14. University of Queensland, Brisbane; 15. Cairns Base Hospital, Cairns; 16. Alice Springs Hospital, Alice Springs; 17. University of Sydney, Sydney; 18. University of Newcastle, Newcastle

The Influenza Complications Alert Network (FluCAN) has operated since 2009, initially as a network of 9 hospitals. The aims are to collect real-time surveillance for influenza requiring hospitalisation and to provide a reliable and timely source of information to inform public health policy. FluCAN determines burden of influenza disease requiring hospitalisation and estimates the effectiveness of influenza vaccine against hospitalisation. In 2014, we expanded this surveillance to include two large specialist paediatric hospitals including Princess Margaret Hospital.

From 3 April until 31 October 2014, 402 children were admitted with PCR-confirmed influenza. Of these, 28% were <1 year, 16% were Aboriginal, and 39% had underlying conditions

predisposing to severe influenza. In those with laboratory-confirmed influenza, Influenza A was detected in 90% of cases; with influenza A(H1N1)pdm09 the most frequent subtype (109/141 who had subtyping performed). The adjusted vaccine effectiveness of one or more doses of TIV for preventing hospitalised influenza was estimated at 47.4% (-0.7%, 72.5%). Effectiveness against influenza A(H1N1)pdm09 was high at 92.2% (40.8%, 99.0%)

Project funding: Commonwealth Department of Health and Ageing

FluMum - a prospective cohort study of mother-infant pairs assessing the effectiveness of maternal influenza vaccination in prevention of influenza in early infancy

Investigators: Kerry-Ann O'Grady¹, Lisa McHugh², Terry Nolan³, Peter Richmond⁴, Caroline Talbot (study coordinator)⁴, Nicholas Wood⁵, Helen Marshall⁶, Stephen Lambert², Mark Chatfield⁷, Ross Andrews⁷

1. Queensland University of Technology, 2. Queensland Children's Medical Research Institute 3. The University of Melbourne; 4. Telethon Kids Institute & UWA School of Paediatrics and Child Health; 5. University of Sydney; 6. University of Adelaide; 7. Charles Darwin University, Darwin

The primary aim of the FluMum Study is to determine the effectiveness of maternal influenza vaccination in pregnancy against laboratory confirmed influenza in infants during the first 6-months of life. Also while conducting

GROUP NAME

this study we aim to;

- Establish the first national system of validated annual influenza vaccine uptake in pregnancy.
- Monitor annual changes in vaccine uptake over time within each of the participating sites.
- Assess the factors that influence the decision to receive influenza vaccination during pregnancy and examine why women are not being vaccinated in pregnancy.
- Estimate the effectiveness of maternal influenza vaccine in pregnancy against laboratory confirmed influenza in the mother during pregnancy and hospitalization of the infant with acute lower respiratory infection (ALRI) during the first six months of life.

10,106 mother-infant pairs will be recruited in six study sites (Darwin, Brisbane, Sydney, Melbourne, Adelaide and Perth) over four consecutive influenza seasons (2012-2015). Assuming equivalent recruitment rates, this will equate to 421 mother-infant pairs per site per year. Over the past three consecutive years Perth has recruited 1162 mother-infant pairs, with the shortfall to be made up in the final year of recruitment next year (2015).

Funding: NHMRC

AusVaxSafety

Investigators: Christopher Blyth^{1,2}, Peter Richmond^{1,2}, Paul Effler², Annette Regan², Lauren Tracey², Tom Snelling²,

Peter Jacoby², Parveen Fathima², Kristine Macartney⁴, Nicholas Wood⁴, Gulam Khandaker⁴, David Durrheim⁵, Craig Dalton⁵, Patrick Cashman⁵, Jody Stevenson⁵, Sally Munnoch⁵, Stephen Clarke⁵, Michelle Butler⁵, Mark Ferson⁵, Deborah Thomson⁵, Keira Glasgow⁵, Lauren Dalton⁵, Stephen Corbett⁵, Salwa Gabriel⁵, Michael Crampton⁵, Katherine Veale⁵, Marina Fulcher⁵, Karen Orr⁶, Kath Canning⁶, Jennifer Murphy⁶, Brendan McMullan⁶, Geraldine Dunne⁶, Jim Buttery⁷, Nigel Crawford⁷, Gowri Selvaraj⁷, Annette Alafaci⁷, Greg Rowles⁸, Peter Eizenburg⁸

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. WA Department of Health; 4. University of Sydney; 5. New South Wales Health, Sydney; 6. The Sydney Children's Hospitals Network; 7. Royal Children's Hospital and Monash Hospitals, Melbourne; 8. General practitioners, Victoria

Building upon the FAST study (2011-2013), this national collaboration undertook a prospective parental survey to identify any significant increase in adverse events following immunization with a seasonal trivalent inactivated influenza vaccine (TIV). In 2014, the parents/carers of children aged 6 months to less than 5 years who received influenza vaccine as part of routine clinical care at sentinel sites in three States (NSW, Victoria and WA) were offered participation in AusVaxSafety surveillance. Information was requested using an SMS message

or email at 3 days after vaccination to parents/carers asking whether the child experienced any adverse event in the time since vaccination.

During the surveillance period (10 March - 15 July 2014) 879 children were enrolled and 782 surveys were completed for 715 (81.3%) children, noting that some parents completed the survey for both dose 1 and dose 2. Data on all 4 vaccine brands registered for use in children was captured; however, the majority of children received the two vaccines funded under the National Immunisation Program, Vaxigrip (86.2%) and Fluarix (10.7%).

Overall 18.4% (95% CI 15.8-21.3%) reported any systemic and/or local adverse events within 3 days of vaccination. Reactions were generally mild and resolved within 1 to 2 days. Of all vaccination encounters in children, 6.8% (95% CI 5.1-8.8%) had fever and 4.3% (95% CI 3.0-6.0%) had injection site reactions. There were only three reports of severe adverse events (SAEs) during the surveillance period; all were in children with elevated temperatures ($\geq 39.5^{\circ}\text{C}$) who also appeared to have concurrent upper respiratory tract infections. All children with SAEs recovered completely within a week. There were no seizures or hospitalisations within the follow-up period.

Project funding: Commonwealth Department of Health, WA Department of Health

Paediatric Active Enhanced Diseases Surveillance (PAEDS)

Investigators: Christopher Blyth¹, Peter Richmond¹, Tom Snelling¹, Chris Robbins (study coordinator) ¹ and Carolyn Finucane (study coordinator) ¹ together with Kristine McCartney², Elizabeth Elliott², Yvonne Zurynski², Peter McIntyre², Robert Booy², Nicholas Wood², Jim Buttery³, Nigel Crawford³, Helen Marshall⁴, Michael Gold⁴, Julia Clark⁵ and Anne Kynaston⁵

1. Princess Margaret Hospital/Telethon Kids Institute; 2. The Children's Hospital at Westmead, Sydney; 3. The Royal Children's Hospital, Melbourne; 4. Women's and Children's Hospital, Adelaide; 5. Royal Children's Hospital, Brisbane

Children's hospitals are uniquely placed to monitor key conditions or complications in childhood infectious diseases. Given the importance of vaccines in preventing childhood infectious diseases, key vaccine preventable conditions and severe side effects from vaccines are monitored in five paediatric hospitals in Australia. These data are used to inform public health authorities and the Australian Immunisation Program.

PAEDS is coordinated by the Australian Paediatric Surveillance Unit (APSU) and the National Centre for Immunisation and Surveillance of Vaccine-Preventable Diseases (NCIRS). There are currently five sites involved across Australia:

- Princess Margaret Hospital for

GROUP NAME

Children (PMH), Perth

- Women's and Children's Hospital, Adelaide
- Royal Children's Hospital, Melbourne
- Royal Children's Hospital, Brisbane
- The Children's Hospital at Westmead, NSW (coordinating centre)

Using hospital-based active surveillance, key vaccine preventable diseases or vaccine-associated adverse events are monitored. Specific conditions are chosen if they are of public health importance and difficult to adequately capturing data through other surveillance mechanisms. The six conditions included as surveillance studies in 2014 were: Acute Childhood Encephalitis, Acute Flaccid Paralysis, Febrile Seizures, Intussusception, Hospitalised Pertussis and Severe Varicella.

Project funding: Commonwealth Department of Health; 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

Investigators: Christopher Blyth^{1,2}, Willie Pomat³, Deborah Lehmann², Rebecca Ford³, Celestine Aho³, Geraldine Masiria³, Joycelyn Sapura³, John Kave³, Tonni Kumani³, Yazid Abdad³, Peter Siba³, Andrew Greenhill³, Paul

Horwood⁴, Ilomo Hwaihwanje², Johanna Wapling², Lea-Ann Kirkham¹, Laurens Manning⁵, Trevor Duke⁶, Peter Richmond^{1,2}

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. PNG Institute of Medical Research, Goroka, Papua New Guinea; 3. Federation University, Ballarat, Victoria; 4. Institut Pasteur du Cambodge, Phnom Penh, Cambodia; 5. UWA School of Medicine and Pharmacology; 6. University of Melbourne

Papua New Guinea (PNG) has the highest rates of child deaths in the Western Pacific Region, with pneumonia, meningitis and septicaemia being the most common causes of death. Earlier studies conducted in PNG have repeatedly demonstrated that most of these infections are caused by the bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, but no detailed studies have been conducted since 1993. The aim of this study is to re-assess which pathogens are currently the most important causes of pneumonia and meningitis in children living in the Highlands of PNG.

In the first 24 months of the study, 576 cases and 473 controls have been enrolled. The majority of children had no known premorbid conditions. Of all children presenting, 346 (60.4%) were admitted to hospital with the remainder managed as outpatients. Of those requiring admission, the median length of stay was 3 days (IQ range: 2 to 5 days). Nine cases died in hospital (9/573: 1.6%) including five with

pneumonia, two with meningitis and two with both pneumonia and meningitis. Through blood cultures, we identified seven patients with H. influenzae type b bacteraemia, fourteen with S. pneumoniae bacteraemia and a further patient with mixed pneumococcal and HiB bacteraemia. One patient had Staphylococcus aureus bacteraemia and a further patient had a non-typhoidal Salmonella bacteraemia. To date, only one cerebrospinal fluid sample was found positive in culture (S. pneumoniae). Serotyping of the invasive pneumococcal species has been performed on all 16 isolates: 56.2% of invasive isolates are vaccine preventable.

Project funding: Investigator Initiated
Research Funds: Pfizer Global

Internal Competitive Research Award
Scheme: Papua New Guinea Institute of
Medical Research

Vaccine Clinical Trials (Vaccine Trials Group)

Our mission is to improve the health of the community through immunisation and the prevention of infectious diseases. Our research teams are evaluating new vaccines and vaccine schedules for a range of infectious diseases through investigator-initiated as well as industry-sponsored trials.

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

Investigators: Peter Richmond^{1,2}, Deborah Lehmann², Peter Jacoby², Denise Anderson², Anita van den Biggelaar², Angela Fuery¹, Peter Siba³, William Pomat³, Andrew Greenhill⁴, Mitton Yoannes³, Christine Opa³, Gerard Saleu³

1. UWA School of Paediatrics and Child Health; 2. Telethon Kids Institute; 3. PNG Institute of Medical Research, Goroka, Papua New Guinea; 4. Federation University, Ballarat, Victoria

Concerns have been raised that administering the 23-valent pneumococcal polysaccharide vaccine (PPV) in infants who first have been vaccinated with pneumococcal conjugate vaccine (PCV) may potentially lead to immunological 'hypo-responsiveness'.

This study aims to determine whether PPV given at 9 months of age:

- 1) provides enhanced persistence of antibody levels protecting against 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

GROUP NAME

4) has an effect on long-term pneumococcal carriage in children primed or not primed with 7vPCV

We are assessing immune function by measuring pneumococcal 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.

Key findings are:

- Pneumococcal carriage rates remain high to age 5 years (>70%) and are predominantly serotypes not included in 7vPCV, irrespective of vaccination history.
- Most children respond to the challenge dose with elevated serotype-specific IgG antibody levels
- In both PPV-vaccinated and unvaccinated children, those who have higher IgG concentrations to start off with respond with lower IgG responses to the challenge
- Children who were immunised with PPV at 9 months of age did not respond with lower IgG response to the challenge dose
- Memory B-cell responses 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

Findings were presented at the

9th International Symposium on Pneumococci and Pneumococcal Diseases in Hyderabad, India in March 2014. A manuscript reporting these findings is in preparation.

Project funding: Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant

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

Investigators: Deborah Lehmann¹, Andrew Greenhill², Peter Richmond^{1,3}, Lea-Ann Kirkham^{1,3}, Peter Siba⁴, William Pomat⁴, Audrey Michael^{4†}, Celestine Aho⁴, Rebecca Ford⁴, Tilda Orami⁴, Vela Solomon⁴, Geraldine Masiria⁴, William Lagani⁴, Trevor Duke⁵, Megan Passey⁶

1. Telethon Kids Institute; 2. Federation University, Ballarat, Victoria; 3. UWA School of Paediatrics and Child Health; 4. PNG Institute of Medical Research, Goroka, Papua New Guinea; 5. University of Melbourne; 6. University of Sydney

Approximately 800,000 children die annually from pneumococcal disease worldwide, 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. 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 distributed in 2014.

The primary aim of this study, which began in November 2011, is to determine whether the 10-valent (PCV10) or 13-valent (PCV13) pneumococcal conjugate vaccines (which include 10 or 13 pneumococcal serotypes, respectively) given in a 1-2-3-month schedule are safe and immunogenic in Papua New Guinean infants. 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 the 23-valent pneumococcal polysaccharide vaccine (PPV) and the other half no PPV. To address the possibility of hyporesponsiveness following PPV, all children will receive a challenge dose (0.1ml) of PPV at age 23 months. Enrolment for this study has been completed, and more than 200 children have completed 9- and 10-month follow-up visits and 140 received a challenge dose at 23 months. The last follow-up at 24 months is due in March 2016. Assays measuring pneumococcal serotype-specific IgG and culture of pernasal swabs have been completed on all samples collected at ages 1 (pre-PCV) and 4 months (one month post-dose 3 PCV).

A total of 1200 pernasal swabs, 1100 serum samples and 630 PBMC samples have been collected to date.

Findings so far are that PCV10 and PCV13 are immunogenic in the early 1-2-3 month schedule in PNG infants, inducing comparable antibody levels and achieving high protective antibody levels at age 4 months. Preliminary results were presented at the Biomedical and Social Sciences Society meeting in Goroka in September 2014.

Project funding:

Exxon-Mobil Governance and Public Affairs

Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant

CHiRRP – Combating Haemophilus influenza related respiratory pathology

Investigators: Kerry-Ann O’Grady¹, Andrew Wilson¹, Peter Richmond^{2,3}, Ruth Thornton^{2,3}, Tanya Stoney^{2,3}, Gabriela Willis^{2,3}, Stephanie Jeffares (study coordinator) ³

1. Queensland University of Technology, Brisbane, 2. UWA School of Paediatrics and Child Health; 3. Telethon Kids Institute

This is a multi-centre, double-blind, randomised controlled trial to evaluate the efficacy of the 10 valent-pneumococcal-Protein D conjugate vaccine Synflorix in reducing respiratory exacerbations in children aged ≥ 18 months and <18 years with

GROUP NAME

suppurative lung disease. Non-typeable *Haemophilus influenzae* is the most common bacterial pathogen associated with exacerbations (cough and infection) in chronic suppurative lung disease (CSLD). The pneumococcal conjugate vaccine Synflorix includes a NTHi Protein D protein carrier. The aim of this study is to establish whether Synflorix through the induction of Protein-D specific immune responses can reduce NTHi-associated infections. In this double blinded randomised controlled trial, children between 18 months and 18 years of age are randomised to receive either the trial vaccine Synflorix or the control vaccine Menactra (Meningococcal ACWY conjugate vaccine). Study sites include Perth, Brisbane, Sydney and Melbourne aiming to enrol a total of 206 children across Australia. We have enrolled 23 children at the Perth site, with recruitment ceasing on August, 2014. Of these 17 have completed all visits, 2 participants have withdrawn from the study and one participant was a screen failure. Three remaining participants in the study are to complete their follow up visits in 2015.

Funders of the project: NHMRC

Follow up of immunogenicity and safety of acellular pertussis vaccine given at birth to 4 years of age

Investigators: Peter Richmond^{1, 2}, Tanya Stoney¹, Gabriela Willis¹, Camille Gibson (study coordinator)¹, together with Nicholas Wood³, Peter McIntyre³, Terry Nolan⁴, Helen Marshall⁵

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. University of Sydney; 4. Urdoch Childrens Research Institute; 5. Women's and Children's Hospital, Adelaide,

This is an open-labelled follow-up study of 97 children who received either an extra dose of pertussis vaccine at birth (4 doses of aP by 12 months of age) or the normal infant immunisation schedule (3 doses of aP by 12 months of age). Children were then randomized to receive an extra booster dose of pertussis containing vaccine at 18 months of age or not. Now at the age of 4 years, the children are again randomized to receive the scheduled normal childhood pertussis containing vaccine (Infanrix-IPV) or the lower dose pertussis containing vaccine (Boostrix-IPV), both together with the schedule Measles, Mumps, Rubella vaccine. Hence there are six different treatment arms in this study.

The aim of the study is to compare the immunogenicity and safety of the normal childhood and low-dose pertussis vaccines when administered to these children at 4 years of age.

Parents of participants who have already received 4 year vaccinations are asked to complete a brief telephone questionnaire about reactions that may have occurred after the 4 year old vaccinations.

So far 11 participants have been enrolled in the 4-year follow up study and 32 questionnaires have been completed.

Funding: NHMRC Project Grant

The vaccine response and long-term antibody persistence of GSK Biologicals' MenACWY-TT vaccine administered as one dose at 6 years post-MenC primary vaccination in healthy subjects aged 12-18 months at primary vaccination

Investigators: Peter Richmond, Jennifer Kent (study coordinator)

Telethon Kids Institute & UWA School of Paediatrics and Child Health

Children who were enrolled in a previous GSK combination vaccine HibMenC (Haemophilus influenza type b / Meningococcal type C) trial when they were 12 months of age and either received the HibMenC combination or separate Hib and MenC vaccines were asked to participate in this follow-up study to evaluate the safety, immunogenicity and duration of antibody persistence of a booster dose of GSK Biologicals' MenACWY-TT (Meningococcal type A, C, W, Y and Tetanus Toxoid) vaccine administered at the age of 7 years. It is expected that the study vaccine will act as a booster for the MenC vaccine and will enlarge the coverage to serogroups A, W135 and Y. The children will be seen at a clinic visit 2 and 4 years after receiving the MenACWY-TT booster vaccine, when a blood sample will be taken to measure the levels of Hib and MenC antibodies. So far 28 children have been re-enrolled in this trial.

Funding: GlaxoSmithKline Biologicals

(sponsor)

A Phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of GlaxoSmithKline Biologicals' meningococcal conjugate vaccine MenACWY-TT in toddlers

Investigators: Peter Richmond, Tanya Stoney, Gabriela Willis, Stephanie Jeffares (study coordinator)

Telethon Kids Institute & UWA School of Paediatrics and Child Health

Meningococcus (Neisseria meningitis) is a bacteria that can cause serious infections leading to meningitis and septicemia. Different strains of meningococci exist. The vaccine trialed in this study protects against four strains of meningococci: types A, C, W and Y, with type C being the only strain that Australian children are currently vaccinated against under the National Immunisation Program at 12 months of age. This study aims to determine whether toddlers should receive 1 or 2 doses of the experimental MenACWY vaccine to induce protective antibody titers, and also whether the vaccine can be given at the same time as the pneumococcal vaccine Prevenar13 without impacting on the safety and efficacy of that vaccine. In Australia Prevenar13 is offered to babies at 2, 4 and 6 months of age as part of the National Immunisation Program. The study involves attending 5 up to 7 clinic visits, depending on whether the child is randomized to receive 1 or 2 doses of

GROUP NAME

the study vaccine, with follow-up visits 1, 3 and 5 years after the last dose of MenACWY.

So far 7 participants have been enrolled

Funding: GlaxoSmithKline Biologicals (sponsor)

A Phase 3, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety and Tolerability of a Meningococcal Serogroup B Bivalent Recombinant Lipoprotein (rLP2086) Vaccine Given in Healthy Subjects Aged ≥ 10 to < 26 Years

Investigators: Peter Richmond, Tanya Stoney, Caroline Talbot (study coordinator)

Telethon Kids Institute & UWA School of Paediatrics and Child Health

This is a phase 3, randomised, active-controlled, observer-blinded trial to assess the safety and tolerability of a Meningococcal Serogroup B Bivalent Recombinant Lipoprotein (rLP2086) vaccine given in healthy subjects aged ≥ 10 to < 26 years old. Subjects in the control group not receiving the experimental vaccine will receive a licensed Hepatitis A vaccine. rLP2086 is given as a 3 dose schedule with the 2nd and 3rd dose being administered 2 and 6 months after the 1st dose respectively (0, 2, 6 month schedule). The control group will receive two doses of Hep A vaccine (2nd dose 6 months after the 1st, i.e. 0 and 6 months) while receiving a normal saline injection two months after the first Hep A dose (i.e. HepA, Saline, HepA) in keeping

with the traditional Hep A vaccination guidelines. Subjects are followed up for 6 months after receiving the 3rd injection.

This study has been completed and we are waiting on the final study report from Pfizer.

Funding: Pfizer (sponsor)

A Randomized, Double-blind, Placebo-controlled, 2-Part Study of Orally Administered ALS-008176 to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Dosing and Multiple Ascending Dosing in Infants Hospitalized with Respiratory Syncytial Virus (RSV) Infection

Investigators: Peter Richmond, Tanya Stoney, Gabriela Willis, Stephanie Jeffares (study coordinator)

Telethon Kids Institute & UWA School of Paediatrics and Child Health

Respiratory syncytial virus (RSV) is one of the viruses causing the 'common cold'. Most babies who get RSV recover fully after 1-2 weeks, but sometimes RSV infections can lead to severe cases of chest infection in children. There are currently no RSV vaccines on the market for the prevention of RSV infection in healthy children, and there are no routinely used medications available for the treatment of RSV. The aim of this two part trial is to study the effects of a new experimental drug called ALS-008176, that is under development by

Alios BioPharma Inc. for use in children infected with RSV. ALS-008176 is an antiviral drug that prevents the virus from dividing and making more copies of itself. The drug is given by mouth as a liquid. ALS-008176 has been tested in adults infected with RSV and demonstrated to significantly reduce the amount of virus and duration, signs and symptoms of RSV infection.

Up to 144 participants will be enrolled into the first part of the study where infants will be given a single dose of ALS-008176. Blood tests, nose swabs and an ECG are also required. This study will take 7 or 8 days to complete. Up to 120 participants will be enrolled into the second part of the study where infants will be given 10 doses of the study drug over 5 days. This study will take 11 or 12 days to complete.

To date 26 Children have been recruited with no safety concerns reported.

Funding: Alios BioPharma Inc (sponsor)

A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP ASO4 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study

Investigators: Rachel Skinner¹, Tanya Stoney², Jane Jones (study coordinator)
2

1. University of Sydney; 2 Telethon Kids Institute

This study is an extension of the HPV-015 research study with GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine for healthy females over 26 years of age. Currently the HPV-16/18 vaccine (Cervarix) is licensed in over 100 countries and is offered free to young women in HPV vaccination programs in the UK and some other European countries. Cervarix was licensed in Australia in May 2007 for women up to the age of 45 years. This study allows women over the age of 45 years, who have participated in the HPV 015 study, to have access to the vaccine if they have not already had it during the course of the study. This study is currently recruiting.

Funding: GSK (sponsor)

Evaluation of a Complex Intervention to Increase Uptake in School HPV Vaccination Program

Investigators: Rachel Skinner¹, Spring Cooper¹, Jane Jones (study coordinator)¹, Helen Marshall², Tanya Stoney³, Kevin McGeechan¹, David Regan⁴ and Patricia Whyte

1. University of Sydney; 2 University of Adelaide; 3. Telethon Kids Institute; 4. University of New South Wales;

The primary aim of this study is to increase the school-based uptake of the human papillomavirus (HPV) vaccination. Secondary aims are to improve program logistical outcomes, knowledge and attitudes, decision

GROUP NAME

making involvement and reduce fear in adolescents receiving the vaccine.

During 2013 and 2014 forty secondary schools across WA and SA participated in this study.

The schools were randomly allocated to the study intervention (receive intervention) or wait-list control (receive intervention the following year). The intervention consisted of adolescent education resources (in-school teaching with teacher training, take home information, app and website for use in schools and out); and methods for distraction/relaxation on vaccination day; an information brochure and decisional support tool for adolescents and parents; and logistical strategies targeting consent form return rates, vaccination-room setup and in-school mop-ups.

Students at participating schools were invited to complete a questionnaire on three occasions throughout the school year (pre and post-vaccination) to determine changes in adolescent knowledge, confidence with vaccination and decision-making. Information about the school vaccination day was also collected by immunisation nurses and supervising school staff on the day. Another aspect of the study is the qualitative component, which helps to “put meaning to the data”. The gathering of this information has been through interviews and focus groups with interested immunisation nurses, students, parents/guardians and school staff who have been involved in the Year 8 immunisation program.

It is hoped that the intervention will have a positive impact on vaccination coverage, adolescent HPV vaccination experience and ease of running the school-based vaccination program.

Funders of the project: NHMRC and bioCSL

Efficacy, immunogenicity and safety study of Clostridium difficile toxoid vaccine in subjects at risk for C. difficile infection

Investigators: Peter Richmond, Tanya Stoney, Gabriela Willis, Camille Gibson (study coordinator)

Telethon Kids Institute & UWA School of Paediatrics and Child Health

This study aims to assess the efficacy of a Clostridium difficile toxoid vaccine in preventing the onset of Clostridium difficile infection (CDI) in adults aged ≥ 50 years who are at risk for CDI and have received at least 1 dose of the experimental vaccine. The study is a randomized, observer blind, placebo controlled, multicentre, multinational Phase III trial recruiting 15,000 subjects in total. Adults aged ≥ 50 years will be enrolled in 1 of 2 risk strata across the treatment groups.

Risk Stratum 1: participant has had at least 2 hospital stays for any condition and each lasting at least ≥ 24 hours in the 12 months before enrolment and has received systemic (not topical) antibiotics in the 12 months before enrolment.

Risk Stratum 2: participant is anticipated to have an inpatient hospitalization for

a planned surgical procedure within 60 days of enrolment.

Participants will be randomly assigned in a 2:1 ratio to receive either the experimental vaccine or placebo. Vaccine or placebo will be administered in a 3 dose schedule on Days 0, 7, and 30. All subjects will be actively followed for efficacy throughout the follow-up period, which may extend for up to 3 years after the last dose.

There have been 14 participants enrolled in the study by the Vaccine Trials Group so far, which is below enrolment target. Recruitment and enrolment have been challenging due to the selection criteria and lack of awareness of CDI within the target population.

Funding: Sanofi Pasteur (sponsor)

Elderly Avian Flu Vaccine Study

Investigators: Peter Richmond (Principal Investigator), Fiona McDonald (study coordinator) & Jane Jones (study coordinator)

Telethon Kids Institute & UWA School of Paediatrics and Child Health

This is a phase II, randomized, observer-blind, multi-centre study to evaluate the safety, tolerability and immunogenicity of two separate doses of an adjuvanted cell culture-derived H5N1 subunit influenza virus vaccine ('bird flu') at two different formulations in healthy elderly subjects. Unlike the conventional egg-based manufacturing process the aH5N1c vaccine is manufactured through cell culture technology.

VTG enrolled twenty-seven participants in this study and all participant-related involvement was completed in 2014. We are currently awaiting the final study report.

Funding: Novartis Vaccines and Diagnostics (sponsor)

Implementation Research

The aim of this team is to ensure that research is translated into strategies that directly improve the wellbeing of children. To achieve this, the team focuses on understanding and evaluating the real world impact of interventions and contextualizing research from other settings to our own population. The team collaborates widely and uses a range of methodological approaches, including pragmatic randomised controlled trials, observational comparative effectiveness studies and data linkage studies. In 2014 the group was awarded over \$4M in competitive research grants for projects that will commence in 2015.

A randomised, placebo-controlled trial of oral nitazoxanide for the empiric treatment of acute gastroenteritis among Australian Indigenous children

Investigators: Tom Snelling¹, Claire Waddington¹, Asha Bowen², Ross Andrews³, Peter Morris³, Mark Naunton⁴, Mark Chatfield³

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health; 3. Menzies School of Health Research,

Darwin; 4. University of Canberra

Aboriginal children continue to experience a large burden of disease from gastroenteritis. Those living in remote settings such as the Northern Territory have a particularly high burden of disease, and frequently require aero-medical retrieval to hospital for management of gastroenteritis. Despite the obvious need, there are still no effective treatment options for acute diarrhoeal illness in children. Management is limited to supportive care with fluid and electrolyte replacement to prevent life-threatening dehydration, correct electrolyte imbalances and improve nutritional status.

Nitazoxanide (NTZ) is a novel antimicrobial that has a broad-spectrum activity against many of the pathogens implicated in acute gastroenteritis in high-burden settings, including in the Northern Territory. In other settings, NTZ treatment has been successfully used to treat gastroenteritis caused by a wide range of pathogens.

Our team successfully obtained an NHMRC project grant in late 2013 to conduct a pragmatic, placebo controlled, randomised clinical trial in the Northern Territory to investigate the potential benefit of using NTZ as an empiric treatment strategy in Indigenous children presenting to hospital with acute gastroenteritis. This study is currently recruiting participants and is planned to continue over the next two years.

Funding: NHMRC project grant 1069772

A randomised control trial of novel treatment strategy for the treatment of bronchiolitis in infants

Investigators: Claire Waddington¹, Tom Snelling¹, Meredith Borland², Andrew Martin², Christopher Blyth^{1,2}

1. Telethon Kids Institute; 2. Princess Margaret Hospital for Children/UWA School of Paediatrics and Child Health

By the time they reach their first birthday, 3-5% of all infants have been hospitalised with bronchiolitis, a condition caused by virally induced inflammation of the lower respiratory tract, resulting in breathing difficulties, cough, poor feeding, irritability and occasionally apnoea. Currently, there are no effective treatments for bronchiolitis, and despite considerable efforts, vaccines for Respiratory syncytial virus (RSV) remain elusive. Expensive prophylactic therapy with RSV monoclonal antibody is of marginal benefit in extremely high risk infants but management is otherwise limited to supportive care with fluids, oxygen and ventilatory assistance, with admission to intensive care units in severe cases.

Novel approaches that are effective, affordable, and well tolerated are desperately needed to reduce the huge morbidity, economic and social burden of bronchiolitis. The broad-spectrum anti-viral activity of a novel anti-infective agent has recently been described, including against the principal viral aetiological agents of bronchiolitis (especially Paramyxoviridae, including

RSV, Human metapneumovirus (hMPV), parainfluenza viruses and the Orthomyxoviridae, including Influenza viruses A and B). As such, this anti-viral treatment may provide a significant and much needed advance in the management of infant bronchiolitis. This project will examine the effect of this treatment compared to placebo on the duration of significant illness in West Australian infants hospitalised with bronchiolitis, to determine if its use as empiric treatment for bronchiolitis is beneficial. Following award a successful funding application in mid-2014, this project is currently in the set-up phase and aims to commence recruitment in winter 2015.

Funding: Telethon-Perth Children's Hospital Research Fund

Determinants of incomplete vaccination and non-vaccination among WA children

Investigators: Claire Waddington¹, Tom Snelling¹, Paul Effler², Julie Leask¹, Hal Willaby³

1. Telethon Kids Institute; 2. Communicable Diseases Control Directorate, WA Department of Health;
3. National Centre for Immunisation Research (NCIRS), Sydney

Safe and effective vaccination is an enormously successful public health intervention. Not only does vaccination protect the individual against disease, it provides population level (herd) protection and brings children into contact with the health system during their most vulnerable years of life.

Incomplete uptake of vaccination remains a problem however, with vaccine preventable diseases (VPDs) still occurring in Australia and other countries despite routine provision of childhood vaccination.

Data from the Australian Childhood Immunisation Register (ACIR) show that vaccination rates in Western Australia (WA) are the lowest for any Australian state with approximately one in ten children incompletely vaccinated.

Determinants of vaccine uptake and timeliness in WA are unknown. A wide range of social, demographic, maternal and infant related factors have been identified as important determinants in other settings but the importance of these factors as determinants in WA is unclear. Understanding determinant factors in WA is critical to identify interventions needed to ensure all children in WA are protected against vaccine preventable disease.

Experience from other states has shown that co-ordinated, targeted approaches can successfully increase vaccination rates. Potential low cost interventions to improve uptake, applicable at a population level, include the use of text message reminders for routine vaccination, and phone calls from health professionals for overdue vaccinations. As well as being effective, the use of modern technologies for vaccination reminder and recall is supported by parents.

This project will identify the determinants of vaccination in WA that will be used design and inform

a targeted approach to increasing vaccine coverage in WA using modern technology (such as the use of text message reminders). The impact of the approach will be assessed in a randomised control trial. These data are an essential step in ensuring that all children in WA are fully protected for vaccine preventable disease.

Project funding: WA Department of Health

The safety and acceptability of mixed whole cell/ acellular pertussis vaccine schedules in infants to prevent sensitisation to food allergens: a pilot study

Investigators: Tom Snelling¹, Peter Richmond^{1,2}, Susan Prescott^{1,2}, Patrick Holt¹

1. Telethon Kids Institute; 2. UWA School of Paediatrics and Child Health

Prior to the widespread use of effective pertussis (whooping cough) vaccines, child mortality from pertussis was significant, and many more children experienced the distressing fits of uncontrolled coughing and gasping that resulted from infection. Despite on-going vaccine programs there has been a concerning resurgence of pertussis in Europe, the United States and Australia, resulting in several neonatal deaths. One factor that may underlie this resurgence is the switch in the late 1990s from using whole-cell pertussis vaccines to more refined acellular vaccines, a move largely driven by data showing that the later had fewer side effects (such as soreness at the

injection site). However, contrary to pre-licensure data, the real-world use of the acellular vaccine appears to result in inferior immunity compared to the use of the older whole cell vaccines.

The best data available indicate that substituting the first infant dose of acellular pertussis vaccine with a single dose of whole cell vaccine could lead to a significant improvement in immune protection against pertussis. Although DTaP has been favoured for its less reactogenic profile, available evidence suggests a single DTwP dose given by 2 months may be only slightly more likely to cause a reaction than a DTaP dose at this age. This project will assess the acceptability and tolerability of this strategy by randomising infants to receive the first pertussis containing vaccine as either DTaP or DTwP in a pilot phase study. If this study provides proof of principal data supporting the idea that a single dose of whole cell vaccine at 2 months of age is acceptable to parents, has an acceptable reactogenicity profile, and results in a favourable immune profile, a much larger multi-centre study safety, immunogenicity and efficacy study will be conducted.

Funding: Telethon-Perth Children's Hospital Research Fund and UWA/WA Health 'near-miss' funding

The role of midwives in tackling vaccine hesitancy

Investigators: Katie Atwell¹, Tom Snelling², Claire Waddington²

1. Murdoch University (Perth, WA);
2. Telethon Kids Institute

Parental hesitancy around the decision to vaccinate their children ('vaccine hesitancy') represents a major threat to public health and our ability to prevent unnecessary deaths from infection. Midwives have an increasingly integral role in immunisation advice and provision, but may abstain from advocating for immunisation for a variety of reasons such as limited understanding of vaccines, lack of access to education resources, or philosophical objections linked to views around bodily autonomy and preference for 'natural' processes. There is evidence that expectant mothers want childhood immunisation information early, which midwives are ideally placed to give. Health care providers, including midwives, have significant influence on parental immunisation decisions. To date, there has been little research on understanding midwives' perspectives and practices on immunisation, and how they might be better engaged as advocates of immunisation for expectant and new parents. This research aims to explore the evidence around the role of midwives in vaccine education and provision, and how vaccination may be optimally framed to resonate with both midwives and their audience of birthing mothers.

Funding: Wesfarmers Centre of Vaccines and Infectious Diseases seed funding

TESTOV Pneumo- evaluation of the effectiveness of the 13-valent pneumococcal conjugate vaccine against pneumococcal pneumonia in children

Investigators: Adam Jaffe¹, Tom Snelling², Stephen Lambert³, Lyn Gilbert⁴

1. University of New South Wales, Sydney;
2. Telethon Kids Institute;
3. University of Queensland, Brisbane;
4. University of Sydney

Streptococcus pneumoniae (pneumococcus) causes a range of infectious diseases, including pneumonia and invasive pneumococcal disease (IPD), and remains a leading cause of childhood morbidity and mortality globally, and is a significant cause of childhood infection in Australia. There are more than 90 different serotypes of *S. pneumoniae*, some of which appear to be more pathogenic than others. Paediatric pneumococcal vaccines provide coverage against a limited number of these serotypes; the 10 valent pneumococcal conjugate vaccine (10vPCV) against 10 serotypes and 13vPCV against 3 additional serotypes (13 in total). Both vaccines are used in Australia's National Immunisation Program (NIP); however, the real world impact of these vaccines on IPD and pneumonia has been mixed, with paradoxical increases in some outcomes, notably for complicated pneumonia. One explanation for this is that vaccination results in a decrease in nasal carriage of vaccine serotypes,

GROUP NAME

opening up a biological niche that allows non-vaccine serotypes to infect ('serotype replacement'). Some of these replacement serotypes may be even more pathogenic than the serotypes they replace. The full impact of the use of conjugate vaccines and serotype replacement has never been fully evaluated.

This study will assess the contribution of *S. pneumoniae* to hospitalisation for pneumonia in Australian children in the post-vaccine era; determine the factors that contribute to these infections; and evaluate the real world effectiveness of the 13vPCV vaccination program in preventing hospitalisation. Children with pneumonia and empyema will be recruited from 13 tertiary paediatric hospitals. Blood, pleural fluid and nasopharyngeal swabs will be tested for *S. pneumoniae* (including serotyping), and other bacteria and respiratory viruses using molecular techniques. The vaccination status of these cases will be compared with matched children from the Australian Childhood Immunisation Registry to determine vaccine effectiveness. It is anticipated that this will be the most comprehensive evaluation of the impact of a national pneumococcal vaccine program on hospitalised pneumonia and that the results will directly influence Australian and international vaccine policy and vaccine development.

Funding: NHMRC project grant

Infectious Diseases Community Reference Group

Institute members: Glenn Pearson (chair), Anita van den Biggelaar, Deborah Lehmann, Hannah Moore, Anke Hoskins, Heidi Hutton and 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 provide input and advice to researchers presenting their proposed research studies to the group and identify 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 2014, presentations covered research projects on rheumatic heart disease, strategies to improve the rates of immunisation in WA, the development of a rapid-test to diagnose bacterial invasive disease, RSV infections in children, and the development of food allergy after whooping cough vaccination.

The CRG, provided feedback on documents intended for study participants and assisted researchers by providing letters of support for specific projects.

Funders of the project: NHMRC Project Grant #572590

Research Support

Dr Anita van den Biggelaar, PhD, MSc

Mrs Marie Abigail Nadal-Sims, BSc (Hons)

Research Theme: Group A Streptococcal Diseases

Head of Group

Professor Jonathan Carapetis, PhD, FAFPHM, FRACP (Infectious Disease), FRACP (Paediatrics), MBBS, BMedSc

Research Staff

Dr Rosemary Wyber, MPH, MBChB

Dr Meru Sheel, PhD, BSc (Biotechnology)

Dr Clancy Read, PhD, GradDip (International Health), BBus

Dr Julie Marsh, PhD

Mr Pdraig Oakley, MPH, BSc

Mr Timothy Johnson, BID

Postgraduate Students

Mr Jeffrey Cannon, PhD candidate

Dr Jess De Dassel, PhD candidate

Dr Daniel Engelman, PhD candidate

Mr David Hendrickx, PhD candidate

Dr Bo Remenyi, PhD candidate

Dr Kathryn Roberts, PhD candidate

Ms Samantha Colquhoun, PhD candidate

Theses passed

Dr Asha Bowen, PhD, Charles Darwin University

Dr Sara Noonan, MSc, Charles Darwin University

External Committees

International

Jonathan Carapetis, Editorial Board Member, Global Heart Journal, World Heart Federation and Elsevier, 2011-current

Jonathan Carapetis, Working Group on Rheumatic Fever and Rheumatic Heart Disease, World Heart Federation, Geneva

Jonathan Carapetis, 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, 2008-current

National

Jonathan Carapetis, Member, Association of Australian Medical Research Institutes (AAMRI), 2014

Jonathan Carapetis, Member, Australian Indigenous Doctors' Association (AIDA), 2014

Jonathan Carapetis, Fellow of the Australian Academy of Health and Medical Sciences (AAHMS), 2014

Jonathan Carapetis, Member, Australian Institute of Company Directors,

GROUP NAME

2012-current

Jonathan Carapetis, Member, Program Management Committee, RHD Australia, 2012-current

Jonathan Carapetis, Board Member, One Disease at a Time Foundation, 2010-current

Jonathan Carapetis, National Committee for Medicine, Australian Academy of Science, 2007-current

Local

Jonathan Carapetis, Member, Department of Corrective Services WA, Youth Justice Board, 2014

Jonathan Carapetis, Member, Western Australian Immunisation Strategy Implementation Steering Committee (WAISISC), 2013-current

Jonathan Carapetis, Chair, Clinical Advisory Group, WA RHD Control Program, 2013-current

Jonathan Carapetis, Member, Western Australian State Health Research Advisory Council (SHRAC), 2012-current

Jonathan Carapetis, Executive Director, Telethon Kids Institute Board of Directors, 2012-current

Invited Presentations

Jonathan Carapetis, Heart Kids WA Keynote, Perth, WA

Jonathan Carapetis, School of Pathology and Laboratory Medicine Seminar Series, Faculty of Medicine and Dentistry, The University of Western Australia, Perth, WA

Jonathan Carapetis, Interscience Conference on Antimicrobial Agents in Chemotherapy (American Society of Microbiology), Washington DC, USA.

Jonathan Carapetis, Public Health Association of Australia, 43rd Annual Conference, Perth, WA.

Jonathan Carapetis, Infection and Immunity in Children International Congress of Paediatric Infectious Disease, Oxford, United Kingdom

Jonathan Carapetis, The World Heart Federation, World Congress of Cardiology Scientific Sessions, Melbourne, VIC

ACTIVE research collaborations

Prof Bart Currie, Menzies School of Health Research, Darwin, NT

Charles Darwin University, NT

Prof Ian Wicks, Walter and Eliza Hall Institute, Melbourne, VIC

Prof Kim Mulholland, Murdoch Childrens Research Institute, Melbourne, VIC

Prof Ben Boyd, Monash Institute of Pharmaceutical Sciences, Melbourne, VIC

Associate Prof Andrew Steer, Centre of International Child Health, Melbourne, VIC

Dr Leisl Zühlke, University of Cape Town, Cape Town, South Africa

Prof John Fraser, University of Auckland, Auckland, NZ

Institute for Health Metrics and Evaluation, Seattle, USA

World Heart Federation, Geneva,
Switzerland

ACTIVE collaborations with industry

Mr Mark Sullivan, Medicines
Development Limited

ACTIVE involvement with the community

Claire Boardman, RHD Australia,
Darwin, NT

Translation

Tools for implementing rheumatic heart
disease programmes (TIPs)

TIPs was launched in May 2014 at
the World Congress of Cardiology
in Melbourne, Australia to define,
describe, and deliver rheumatic
heart disease control programs.
The handbook is a compilation of
implementation experience from
peer reviewed and grey literature.
The resource is intended for program
managers and policy makers to deliver
priority-based rheumatic heart disease
control programs.

Research Theme: Ear Health

Group Leader

Associate Professor Peter Richmond,
MBBS, MRCP, FRACP

Research Staff

Associate Professor Deborah Lehmann,
MBBS, MSc

Dr Lea-Ann Kirkham, PhD, BSc (Hons)

Dr Ruth Thornton PhD, BSc (Hons)

Mrs Victoria Stroud, MSc (Speech
Pathology, BSc (Hons)

Postgraduate Students

Ms Emma de Jong, PhD candidate

Ms Stephanie Trend, PhD candidate

Ms Tulia Mateus, PhD candidate

Awards

Ms Emma de Jong, Preterm Infants
Centre of Research Excellence top-up
scholarship

Ms Janessa Pickering, Australian otitis
media conference (OMOZ) travel award
2014

Ms Tulia Mateus, International Post-
Graduate Research Scholarship (IPRS)
APA

External Committees

International

Deborah Lehmann, Papua New
Guinea Institute of Medical Research
Buttressing Coalition, 1998-current

Deborah Lehmann, Member of
Conference Committee for the 19th
International Symposium on Recent
Advances in Otitis Media (RAOM),
2012-current

National

Deborah Lehmann: Data safety
monitoring board of CHiRRP
“Combating H. influenzae related
respiratory pathology” (2012-current)

Local

GROUP NAME

Deborah Lehmann, Meningitis Centre Management Committee (1998-current)

Deborah Lehmann, Infectious Diseases Community Reference Group (2008-2014)

Deborah Lehmann, Dissolving the glue in glue ear: Assessment of the use of Dornase alfa as an adjunct therapy to ventilation tube insertion, 2013 -current

Invited Presentations

Peter Richmond, Australian Otitis Media Conference (OMOZ), Melbourne, Vic, Aug 6-8 2014

Peter Richmond, The Australian and New Zealand Society of Paediatric Otorhinolaryngology, Annual Scientific Meeting. Bunk Bay, WA, Oct 2014

Deborah Lehmann, Community Ear and Hearing Health Forum, Broome, WA, May 14-16 2014 Deborah Lehmann, Australian Otitis Media Conference (OMOZ), Melbourne, Vic Aug 6-8 2014

Heidi Hutton, Child and Adolescent Health Research Symposium, Perth, WA, Oct 22-24 2014

Janessa Pickering, Australia Otitis Media Conference (OMOZ), Melbourne, Vic, Aug 6-8 2014

Stephanie Jeffares, Australia Otitis Media Conference (OMOZ), Vic, Aug 6-8 2014

Active research collaborations

David Smith, PathWest Laboratory Medicine, Perth WA

Anne Mahony, Population Health, WA

Country Health Services – Goldfields 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

Paul Effler, Carolien Giele Communicable Disease Control Directorate, Department of Health, Perth WA

Ngunytju Tjitji Pirni Inc, Kalgoorlie WA

Bega Garnbirringu Health Services, Kalgoorlie, WA

Allan Cripps, Gold Coast Campus, Griffith University, Qld

Eileen Dunne, Catherine Satzke, Murdoch Children's Research Institute, Melbourne Vic

Megan Passey, University Centre for Rural Health-North Coast, University of Sydney

Sanjay Jayasinghe, National Centre for Immunisation Research and Surveillance for Vaccine Preventable Diseases, Sydney, NSW

Kylie Carville, Victorian Infectious Diseases Reference Laboratory, Melbourne

ACTIVE collaborations with industry

CSL, Australia – supply of Pneumovax for pneumococcal vaccine trials in PNG

Research Theme – Infectious Diseases Epidemiology & Surveillance

Group Leaders

Dr Hannah Moore, BSc (Hons1),
GradDipClinEpid, PhD

Associate Professor Christopher Blyth,
MBBS (Hons) DCH FRACP FRCPA

Research Staff

Ms Faye Janice Lim; BSc, BA, BMedSci
(Hons)

Ms Parveen Fathima; BDS, M Infect Dis

Ms Tasnim Abdalla; BSc, MPH

Postgraduate Students

Faye Janice Lim, PhD candidate

Alicia Annamalay, BSc Hons

Awards

Hannah Moore; Telethon Kids Institute
PhD Supervisor of the Year Award

Hannah Moore; Australian Academy
of Science/Science and Industry
Endowment Fund Fellowship to attend
64th Meeting of the Nobel Laureates in
Lindau, Germany

Hannah Moore; New Independent
Researcher Infrastructure Support
(NIRIS) Award

Faye Janice Lim; Finalist, The University
of Western Australia 3-Minute-Thesis

Heats

Faye Janice Lim; 1st prize, Telethon
Kids Institute 8th Annual Student Circle
Symposium

External Committees

International

National

Chris Blyth, Australian Technical
Advisory Group on Immunisations
(ATAGI) Australian Government:
Department of Health and Aging,
Deputy Chair (2014- Current)

Chris Blyth, ATAGI/CNDA Rabies
Working Party Australian Government:
Department of Health and Aging, Chair
(2014 – Current):

Chris Blyth, ATAGI Varicella / Zoster
Working Party Australian Government:
Department of Health and Aging, (2013
– Current)

Chris Blyth, ATAGI Pneumococcal
Working Party Australian Government:
Department of Health and Aging,
Member (2013 – Current)

Local

Hannah Moore, Telethon Kids Institute
Early Environment Research Focus Area
Steering Committee

Hannah Moore, Telethon Kids Institute
Early-Mid Career Research Council

Chris Blyth, WA Tuberculosis Advisory
Council Health Department of Western
Australia

Invited Presentations

Hannah Moore, Data Linkage

GROUP NAME

Roundtable, Wollaston College, Perth, WA, Nov 2014

Chris Blythe,. Perinatal Society of Australia and New Zealand Annual Conference, Perth, WA 2014

Chris Blyth, Influenza Specialist Group Annual Scientific Meeting, Melbourne, Vic, 2014

Faye Janice Lim, Endeavour College of Natural Health, Perth, WA Aug 26, 2014

ACTIVE research collaborations

Dr Kathryn Glass, National Centre for Epidemiology and Population Health, Australian National University, Canberra ACT

Drs Heather Gidding and Bette Liu, School of Public Health & Community Medicine, University of New South Wales, Sydney, NSW

Dr Pia Hardelid and Professor Ruth Gilbert, Institute for Child Health, University College London, UK

Prof Peter McIntyre, National Centre for Immunisation Research and Surveillance, Sydney NSW Prof David Smith, PathWest Laboratory Medicine, Perth WA

Dr Anthony Keil, PathWest Laboratory Medicine and Department of Microbiology, Princess Margaret Hospital, Perth WA

Prof David Burgner, Infection, Immunity & Environment, Murdoch Children's Research Institute, Melbourne Vic Dr Paul Effler, Communicable Diseases Control Directorate, WA Department of Health, Perth WA

Dr Tobias Strunk, Consultant neonatologist at King Edward Memorial and Princess Margaret Hospitals, Perth WA

Prof Trevor Duke, Centre for International Health, University of Melbourne, Vic

Prof Peter Siba , Dr William Pomat, Mrs Rebecca Ford, Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea

Dr Andrew Greenhill, Federation University, Churchill Campus, Vic

ACTIVE involvement with the community

Hannah Moore, Infectious Diseases Community Reference Group, Telethon Kids Institute, Perth, WA

Research Theme – Vaccine Clinical Trials (Vaccine Trials Group)

Head of Group

Associate Professor Peter Richmond, MBBS, MRCP(UK), FRACP

Research Staff

Camille Gibson, BSc (Nursing), BSc (Environmental Health)

Caroline Talbot, Certificate IV Enrolled Nursing

Caroline Wharton, EN Cert IV

Carolyn Finucane, Registered Nurse

Christine Robins, Enrolled Nurse

Fiona McDonald, BSc (Nursing)

Heidi Hutton, BSc (HMvt), DipEd, MSc
Jacqueline Connell, Registered Nurse
Jan Jones BSc (Hons) Dip.Ed
Jane Jones, BSc Nursing, BSc
Environmental Science (Hon)
Jennifer Kent, Registered Nurse
Karli Corscadden, BSc (Hons)
Lisa Montgomery
Stephanie Jeffares, BSc (Nursing),
Immunisation Course Certificate (ECU,
2004)
Susan Patoir, B.Pharm, Registered Nurse
Ushma Wadia, MBBS, FRACP

National Committees

Peter Richmond, Deputy Chairperson,
Australian Technical Advisory Group on
Immunisation (ATAGI), Commonwealth
Department of Health and Ageing,
2010-2014

Peter Richmond, Chair, ATAGI MMR-
Varicella and Herpes Zoster Vaccine
Working Party, 2006-current

Peter Richmond, Member, ATAGI
Pneumococcal Vaccine Working Party,
2007-current

Peter Richmond, Member, Steering
Committee PTNA (Paediatric Trials
Network of Australia), 2010-current

Peter Richmond, Member, ATAGI Hib
and meningococcal C Vaccine Working
Party, 2008-current

Peter Richmond, Member, ATAGI
H1N1 Influenza Vaccine Working Party,
2009-current

Local Committees

Peter Richmond, New Children's
Hospital Research and Education
Reference group (Chair), 2009

Peter Richmond, Child Health Research
and Education Advisory Committee
(Chair), 2009

Peter Richmond, Child and Adolescent
Health Service, Activity Based Funding
Steering Committee, 2012

Invited Presentations

Peter Richmond, 9th International
Symposium on Pneumococci and
Pneumococcal Diseases. Hyderabad,
India, Mar 2014

Peter Richmond, Crucell J&J Bacterial
Advisory Board meeting. Antwerp,
Belgium, April 2014

Peter Richmond, Australian Vaccines
and Immunotherapeutics Development
meeting. Melbourne, Vic, May 2014

Peter Richmond, Papua New Guinea
Biomedical and Social Sciences Society
Specialty meeting. Goroka, PNG, Sept
2014

ACTIVE collaborations with industry

WA Department of Health

Commonwealth Department of Health
and Ageing

Safe Vic

Balance Therapeutics

Pfizer

Novartis

GlaxoSmithKline

GROUP NAME

Sanofi Pasteur

ACTIVE involvement with the community

Heidi Hutton, Infectious Diseases
Community Reference Group

Peter Richmond, Pregnancy, Babies and
Children's Expo – "The Good Oil on
Immunisation: what do I need to know?",
Perth, WA, Aug 2014

Peter Richmond, Women's and
Children's Health Update, Healthed.
The University of Western Australia,
Perth, WA, Aug 2014

Peter Richmond, South Australian
Vaccinology Update, Robinson
Research Institute, Adelaide, SA, Oct
2014

Nestle Paediatric Immunisation Seminar
- "New options for prevention of
respiratory infections", South Perth, WA,
Nov 2014

Research Theme – Implementation Research

Group Leader

Dr Tom Snelling, PhD, FRACP

Research staff

Dr Claire Waddington, DPhil, MRCP (UK)

Dr Julie Marsh, PhD

Mrs Katie Atwell, PhD

Mrs Yue Wu, PhD (submitted)

Mr Charlie McLeod, BMBS

Research support

Ms Natalie Eiffler

Ms Ellen Tapsell

Ms Jessica Edmeades

Awards

Tom Snelling, Raine Clinical Research
Fellowship

Claire Waddington, Friends of the
Institute travel award

Claire Waddington, ESPID ADVAC
Fellowship

Claire Waddington, ADVAC prize in
vaccinology

Claire Waddington, Telethon Clinical
Research Fellowship

Marie Estcourt, Allergy CRE Fellowship

External Committees

National

Tom Snelling, Pharmaceutical
Benefits Advisory Committee (PBAC),
2014-current

Tom Snelling, Economics Sub-
Committee of the PBAC

Local

Tom Snelling, Aboriginal Health
Research Focus Area steering
committee, Telethon Kids Institute, co-
chair

Tom Snelling, Antimicrobial stewardship
committee chair, Princess Margaret
Hospital

Tom Snelling, WA Committee on
Antimicrobials, WA Health

Tom Snelling and Claire Waddington, Biological Hazards Committee, Telethon Kids Institute

Tom Snelling and Claire Waddington, WA ACTA

Invited Presentations

Tom Snelling, Methods in vaccine effectiveness and safety workshop, Sydney, NSW, Oct 28 2014

Tom Snelling, HIV Update, Sydney, NSW, Oct 23 2014

Tom Snelling, Australian Society for Infectious Diseases Annual Conference, Adelaide, SA, March 26 2014

Tom Snelling, PHAA Annual Scientific Meeting, Canberra, ACT, Mar 2014

Claire Waddington, Biological challenges to effective vaccines, Royal Society, UK, Nov 2014

ACTIVE research collaborations

Katie Atwell, Murdoch University, Perth, WA

Ross Andrews, Charles Darwin University, Darwin, NT

Rob Baird, Royal Darwin Hospital, Darwin, NT

Meredity Borland, Princess Margaret Hospital, Perth, WA

Dianne Campbell, University of Sydney, Sydney, NSW

Mark Chatfield, Menzies School of Health Research, Darwin, NT

John Crump, University of Otago, New Zealand

Nigel Cunliffe, Murdoch Childrens' Research Institute, Melbourne, Victoria

Margie Danchin, Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC), Victoria

Paul Effler, WA Department of Health, Perth, WA

Lyn Gilbert, University of Sydney, Sydney, NSW

Prof Michael Gold, The Women's and Children's Health Network, Adelaide, SA

Patrick Holt, Telethon Kids Institute, Perth, WA

Adam Jaffe, University of New South Wales, Sydney, NSW

Carl Kirkwood, Murdoch Childrens' Research Institute, Melbourne, Vic

Julie Leask, University of Sydney, NSW

Andrew Martin, Princess Margaret Hospital for Children, Perth, WA

Peter McIntyre, University of Sydney, NSW

Peter Morris, Menzies School of Health Research, Darwin, NT

Mark Naunton, University of Canberra, ACT

Andrew Pollard, University of Oxford, UK

Susan Prescott, Telethon Kids Institute, Perth, WA

Tom Riley, University of Western Australia, Perth, WA

Roy Robins-Browne, University of Melbourne, Vic

GROUP NAME

Nick Wood, University of Sydney, NSW

ACTIVE involvement with the community

Tom Snelling, 'Baby Expo', Claremont Showground, WA

Changes to clinical practice

Tom Snelling, PMH antimicrobial stewardship program

Tom Snelling and Claire Waddington, literature review to inform the update of the CARPA manual for the management of gastroenteritis

Health policies and guidelines directly influenced

Claire Waddington, European Medicines Agency's review on the role of challenge studies in vaccine licensure (July 2014)

Other achievements

The Implementation team was awarded three NHMRC grants in 2014 (as either CI-A or AI), accounting for >\$5M of NHMRC research funding starting in 2015



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PRINCIPAL PARTNER



STRATEGIC PARTNER

