INFECTIOUS DISEASE RESEARCHER
DR DEBORAH LEHMANN WITH RILEY

Telethon Institute for
Child Health Research

ANNUAL REPORT 2011
SCIENTIFIC SUPPLEMENT

Delivering hope through life-changing research

PRINCIPAL PARTNER

telethon 7

Telethon Institute for
Child Health Research

Contents

Delivering hope through life-changing research

How does a research organisation deliver hope?

It is through medical research that one day there will be a cure for children's cancers and asthma.

It is how better treatments are developed for children with cerebral palsy and how it was discovered that a vitamin – folate – could prevent many cases of spina bifida.

We know that when a child is born with or develops a serious disease or disability, their families look to medical research to give them hope for the future.

It's a responsibility we take very seriously.

At the Telethon Institute for Child Health Research, our community not only actively participates in our research projects but informs and shapes what we do through our Consumer and Community Advisory Council and Community Conversations.

Our Annual Report is part of our commitment to share more about the research that we are currently doing.

We also have a new, easy to navigate website with an index of every project currently underway – just use the search button and type in your key words.

In this Scientific Supplement you will find complete scientific research reports from 2011. For our general annual report, please visit our website.

Find our more at **www.childhealthresearch.org.au**

ABORIGINAL HEALTH RESEARCH

The Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW)

Overview

The Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW) is a strategic program of intervention research that is focused on achieving radical and sustainable change for the Aboriginal community and improving the lives of Aboriginal people. The program is a unique validation of Aboriginal knowledge and demonstration of Aboriginal methodology involving a multi-disciplinary team of Aboriginal and non-Aboriginal researchers, who will contribute to the body of knowledge, work transparently with the Aboriginal community and embrace Aboriginal culture and ways of thinking.

The CREAHW brings the research strengths of each of the Chief Investigators together in a cohesive program of community-based intervention research, well known both nationally and internationally, but with local relevance to Western Australia. It will be supported by the outstanding track record of the Telethon Institute for Child Health Research in working with government and informing policy and practice and build on past achievements by developing the next generation of Aboriginal health researchers and leadership among the Chief Investigator team.

The CREAHW team program of research will build capacity in the community and bridge the disconnection between researchers, service providers and the community in a practical and empowering way. History has seen significant issues, such as racism, perpetuated and become embedded in the Aboriginal community with a significant negative impact on health and wellbeing. The CREAHW investigators are seeking to change this cycle by listening and working in partnership with the community and investing energy and attention to get the best result for the community. This will require system change and involve investing time with decision makers in order to inform policy and practice.

Funders of the project: In 2010, the National Health and Medical Research Council awarded the Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW) grant to a group of 10 Chief Investigators (CI) headed by Professor Fiona Stanley AC (Director, Telethon Institute for Child Health Research). The CREAHW is a collaborative research venture between seven research institutions, and is funded with a grant of $2.5m over five years.

Sub projects within the CREAHW:

The CREAHW has several Chief Investigators and their individual and collaborative research projects aim to answer specific research and policy relevant questions within Aboriginal Health and Wellbeing. Projects being undertaken by researchers at the Telethon Institute are as follows:

LOOKING FORWARD: IMPROVING MENTAL HEALTH SERVICE OUTCOMES FOR ABORIGINAL PEOPLE LIVING IN THE SOUTH-EAST METROPOLITAN CORRIDOR

Michael Wright, Fiona Stanley

This project is a partnership between Aboriginal families[1], government and non-government mental health service providers, primary health-care providers (GP's) Aboriginal Medical Service, and the Telethon Institute for Child Health Research.

The goal of this project is to increase the effectiveness of the public mental health services for Aboriginal families whose lives are affected by serious mental illness living in the south-east metropolitan corridor. The project will engage service users, Aboriginal and non-Aboriginal service providers, policy makers and managers.

The project aims to develop in consultation with service users (Aboriginal families) and service providers a culturally safe mental health framework that will assist in the delivery of mental health services to Aboriginal families living in the south-east metropolitan region.

The methodology for the project includes conducting a series of community forums across the region. The forums commenced in March 2011 and will extend for a period of 18 months, finishing in July 2012. A report will be published and released at the end of 2012. The project is expected to be completed at the end of 2013.

Funders of the project: NHMRC are funding the lead researcher.

IMPLEMENTING THE AEDI IN THE WESTERN DESERT

Roz Walker

The key objective of this research project is to improve the maternal and child health and wellbeing of Martu communities living in the Western Desert communities of Jigalong, Punmu, Parngurr and Kunawarritji and Newman in the Pilbara. The project is undertaken in partnership with funding through BHP Billiton Iron Ore, Indigenous Community Investment Program 2010-2014. Using Community-based Participatory Action Research methods the project provides the evidence base and conceptual underpinnings to inform and evaluate the new maternal and child health initiatives being developed by World Vision Australia and other stakeholders to improve the social, educational and maternal and child health and wellbeing outcomes of the Western Desert communities.

Specifically the project involves implementing, communicating and disseminating the AEDI results to relevant stakeholders in health and education Aboriginal across the Western Desert communities over the five years 2010-2014. It also involves trialling appropriate tools and communication strategies to share the information with Aboriginal families to build of their knowledge and strengthen community capacity. There is strong research evidence which confirms the benefits of using the Early Development Index to bring about

community level change in Australia and in Canada.

CONNECTION, BELONGING AND HEALTH OF AUSTRALIAN ABORIGINAL PEOPLE AND THEIR COMMUNITIES IN THE CITY OF SWAN AND THE PILBARA REGION OF WESTERN AUSTRALIA.

Rhonda Marriott, Fiona Stanley, Nick de Klerk, Cheryl Kickett-Tucker, Roz Walker & Denise Groves

This holistic, 4 year qualitative study will explore the relationship between connection and belonging for Aboriginal people living in the City of Swan and the Pilbara with health outcomes to develop a conceptual framework. This important and original work will add to the paucity of knowledge in this area. The researcher will apply a community participatory action research approach and thus, engage with the community at all steps in the research project. A conceptual framework will evolve from the research data and this will be applied to selected health priorities: for example, the relationship of Aboriginal spirituality and birthing on country. The work will also test the phenomenological variant of ecological systems theory (PVEST) (Spencer, Dupree and Hartman, 1997; Spencer, Fegley and Dupree, 2006) in understanding cultural resilience and its relationship with connection, belonging and health. This important and original work will add to the paucity of knowledge on resilience and health outcomes. Recommendations will drive health policy; build community resilience and capacity; inform non-Aboriginal health care professionals' understanding of the need for culturally appropriate health care services; guide health professionals' practice; and guide health policy for the provision of culturally appropriate health services.

STRENGTHENING SOCIAL AND EMOTIONAL WELLBEING OF AUSTRALIAN ABORIGINAL PEOPLE: HOW DOES RACIAL IDENTITY AND RELATED SELF-ESTEEM MEDIATE THE MENTAL WELLBEING OF ABORIGINAL PEOPLE?

Cheryl Kickett-Tucker

This is an extension of Cheryl Kickett-Tucker's research on the development of racial identity and related self-esteem of Aboriginal children, youth and adults (using her IRISE measures across the life span). This research will describe the mediating factors of racial identity and related self-esteem in relation to Aboriginal people's mental wellbeing and identify effective ways to strengthen the social, cultural and emotional wellbeing and identity of Aboriginal children, youth and young adults onwards. This research will encompass development of new instrumentation, complemented by in depth personal interviews using Community Participatory Action Research (CPAR) methods.

CONSULTING WITH THE COMMUNITY TO DEVELOP AN INNOVATIVE AND CULTURALLY RESPONSIVE EMPOWERMENT, HEALING AND LEADERSHIP PROGRAM

Pat Dudgeon, Roz Walker, Clair Scrine, Cheryl Dunkley, Divinna D'Anna, & Kathleen Cox

The project is being done in collaboration with Kimberley Aboriginal Medical Services Council (KAMSC) Social Emotional Wellbeing Unit. This project stems from the high rates of Suicide in the Kimberley in 2010. The aims of this project are to strengthen the capacity of community members to empower themselves and others to change their lives, their communities and the systems that are barriers to good social and emotional wellbeing. The findings will be used to develop an accredited innovative program that is culturally appropriate to the empowerment of Aboriginal people in different geographical locations. The project consists of the following two stages - community and stakeholder consultation; program development.

CULTURAL SECURITY FOR YAMAJI (ABORIGINAL PEOPLE) WITHIN HEALTH SERVICES IN THE MIDWEST MURCHISON REGION OF WESTERN AUSTRALIA.

Juli Coffin

This project aims to create a culturally secure health service for Yamaji (Aboriginal people) in the Midwest/Murchison region of Western Australia. This will be achieved through the mapping of current policies and practices when treating and engaging Aboriginal health consumers across all health sectors, implementation of the 'Cultural Security Framework' (Coffin 2007) within each health sector to show the strengths and weaknesses for priority, and working within each health sector to create strategies/policies and practice to improve areas of weakness.

It is hoped that this project with provide evidence that changes can be culturally secure and sustainable. This project will also take into consideration the existing Department of Health Cultural Respect Implementation Framework and other documentation/policies in regard to this issue. An arm of the Cultural Security project in the North Metropolitan region has also been established through the PindiPindi Centre as part of improving culturally secure health service delivery to Aboriginal people in the North Metropolitan Health Service Area. This will ensure great research translation across rural, remote and urban settings of the proposed methodology and model. The Framework strategies and actions will be developed by the Cultural Security Aboriginal Leadership Group; this group will provide practical implementation guidance and cultural advice to the program.

WESTERN AUSTRALIAN ABORIGINAL INTERGENERATIONAL FETAL GROWTH STUDY (WAAIFS)

Sandra Eades, Bridgette McNamara, Glenn Pearson, Amanda Langridge, Carrington Shepherd, Nicholas de Klerk & Fiona Stanley

This project will investigate determinants of fetal growth across generations, in all Aboriginal mothers and children born in Western Australia between 1980 and 2009, using a novel measure of fetal growth; the percentage of optimal birth weight (POBW). POBW measures the appropriateness of fetal growth for a given gestational age, fetal gender, maternal height and parity, and allows the prevalence and severity of both growth restriction and excessive

growth to be assessed.

Using unique data from linked administrative health datasets spanning over 30 years and multilevel models, the study will map the differing contributions of fetal growth to chronic diseases in individuals, the links between maternal fetal growth and that of her offspring, and how the occurrence of medical conditions and pregnancy complications influences that relationship. We will explore the causal pathways involved in the perpetuation of sub-optimal fetal growth across generations, as well as those that are protective.

These investigations will be to inform whether the most important pathways to chronic disease began in grand-maternal environments or in the next generation. The results are likely to provide evidence for when maternal and child health interventions are likely to be most effective for the prevention of lifelong adult diseases including those influencing reproductive risks.

FAMILY ASSESSMENT TOOL, MILLIYA RUMURRA, BROOME

Dawn Bessarab

Milliya Rumurra (MR) is a residential centre providing treatment and rehabilitation to Indigenous community members wishing to address their misuse of alcohol and other drugs (AOD). Currently as part of their formal program MR assess all individuals attending the centre to develop a specific treatment plan to assist each person in addressing their AOD use while they are at the centre. The centre's outreach program informally works with the family of the attending person to help them to understand what the centre is offering and to provide support while their member is receiving treatment. The outreach program also assists both the family and the client with their transition back into the family and community on completion of the program.

When looking at the health and social and mental well-being of their clients MR now want to integrate the support service that they offer to the families of their clients and develop a family assessment tool that can more effectively help their workers in developing a specific case plan that engages with the family during the rehabilitation process of their member. The current project is to work with the management, clinical and outreach team, clients, families, community members and service stakeholders to develop a family assessment tool. This tool will become an integral part of the MR's service and will be used by clinical and outreach team workers to assess the needs of the client's family at the time of intake. The project will utilize the community based participatory research approach. The aim of the assessment tool is to improve the health and quality of the Aboriginal client and their family during their journey through AOD treatment. The final outcome of the project will be the development of a family assessment tool which will be trialled by MR's clinical and outreach team and evaluated for its usefulness and effectiveness.

Kulunga Research Network

Overview

The aims of the Kulunga Research Network are to (1) facilitate high quality research that is community based and culturally safe, (2) to develop the capacity of Aboriginal and non-Aboriginal people to conduct high quality research with Aboriginal communities, (3) to facilitate the translation of research into policy and practice and (4) to act as an advocate for Aboriginal families in public policy development. In addition to progressing its research projects, the focus of the team in 2011 has been on building relationships with communities and community-based organisations, and assisting government and non-government organisations to work effectively with Aboriginal people and ensure their messages are appropriate and effective. In addition, staff have been working collaboratively across TICHR with a number of projects.

EXAMINING THE CRITICAL FACTORS IN ABORIGINAL NON-SMOKING

Clair Scrine, Rose Murray

The Kulunga Research Network was engaged by the Cancer Council (WA) to ascertain reasons why some Aboriginal people have never taken up smoking and how other Aboriginal people have successfully quit. Results were sought to better inform future health promotion campaigns and projects targeting Aboriginal families in regional and metropolitan communities. The research sought to explore people's motivations and experiences as a non-smoker and successful quitter. It sought to document the personal circumstances of individuals as well as examining the role of more common issues including family and social, economic, and cultural influences that exist around tobacco use among Aboriginal adults in contemporary Western Australia.

A qualitative research process was utilised in order to facilitate an understanding of the complexity of people's experiences and circumstances and allow participants to tell their story. The research found that people chose not to smoke and to quit for a number of reasons. Many factors including family, social norms, group dynamics and peer pressure act as both supports and barriers to people's quitting and in influencing whether people chose to smoke or not. The research found an observable strong sense of self among the participants which seemingly underpinned their actions and their ability to remain strong as a non-smoker or effective quitter. Both non-smokers and successful quitters spoke with pride of their achievement at not smoking knowing that they were improving their personal and extended family health through their actions. The sense of achievement was especially notable among the quitters, despite the pressures some experienced from friends and family in their attempts to quit and in their stance against smoking.

Funders of the project: The Cancer Council WA

ADDRESSING ABORIGINAL RATES OF ORGAN DONATION

Clair Scrine, Rose Murray

This project sought to have a greater understanding of the cultural barriers and perceptions regarding organ and tissue donation among Aboriginal people, and identify the barriers some Aboriginal people experience or perceive with the current organ donor registration process. It also sought to work to increase Aboriginal people's understanding of the critical need for donation and raise awareness and understanding among Aboriginal people about the need and processes involved for organ and tissue donation. Finally the project sought to provide accurate information to enable Aboriginal people to promote family discussions and to develop messages about donation for use in their local community. Key findings included differing ideas and cultural beliefs about donation; a notable lack of understanding and limited knowledge about the process of donation and registering to donate among Aboriginal people consulted; a real lack of awareness of the emphasis on discussing the issue with family and current campaigns regarding donation; a high level of mistrust and fear of medical professions, institutions and procedures among Aboriginal people which are impacting on people's views about donation; the need for appropriate educational aids and resources to facilitate discussion and understanding about donation among Aboriginal people.

Funders of the project: This research was funded by an Organ and Tissue Authority 'Community Awareness Grant'.

EVALUATION OF THE MICHAEL LESLIE PILBARA PERFORMING ARTS PROGRAM

Clair Scrine, Rose Murray

The evaluation assessed the Michael Leslie Pilbara Performing Arts Program against its core objectives of enabling improved educational attainment, self-esteem and aspiration in its Aboriginal and non-Aboriginal students. It found that the impact of the program is consistent with much of the literature on the positive impact of young people's involvement in the performing arts on their self-esteem, confidence, learning, and motivation. Through a qualitative research process, the project found that participation in the program can be a transformative experience that brings about significant changes in students' lives. The program provides students with skills and experience that can assist them to collaborate, be disciplined both physically and mentally, be expressive, listen and respond, and take personal risks, complete a complex task and then perform it in front of peers - all highly valuable and transferable skills that are important in a range of contexts including a learning environment. The program's focus on youth engagement and youth participation provides a range of students with skills necessary for fostering qualities of leadership and different styles of communication amongst their peers and communities. Similarly, the program increases cultural pride and self-determination which, in turn, encourages students to take leadership of their life, their family, and their community. The impact of the program on students' self-esteem and aspirations is particularly significant given the evidence on the importance of positive self-esteem to children and young people's healthy lives and futures. A series of recommendations were also made concerning ways to enhance the program's effectiveness and increase the number of students accessing its benefits.

Funders of the project: This project was funded by a Healthway 'Health Promotion Research Starter Grant'

TREADING CAREFULLY: SOCIO POLITICAL IMPLICATIONS OF GENETIC RESEARCH IN ABORIGINAL AND TORRES STRAIT ISLANDER COMMUNITIES

Emma Kowal, Glenn Pearson

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

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

This project commenced as a post-doctoral research project (has subsequently received an NHMRC grant) and is being led by Dr Emma Kowal from the University of Melbourne

WORKING TOGETHER: ABORIGINAL AND TORRES STRAIT ISLANDER MENTAL HEALTH AND WELLBEING PRINCIPLES AND PRACTICE

Roz Walker (Project Leader), Glenn Pearson (Manager, Kulunga), Jacqueline Ann Bradley (Communications Project Officer), Pat Dudgeon, (Expert Consultant), and Clinton Shultz, (Indigenous Consultant).

Working Together was produced as an important resource to improve the capacity of Aboriginal and non-Aboriginal health workers, mental health workers and relevant practitioners to identify and address mental illness and associated issues of substance misuse and suicide in Aboriginal and Torres Strait Islander communities, to recognise the early signs of mental illness and make referrals for treatment where appropriate. It is also intended for staff working in Healing Centres and Link-up agencies to address issues of grief, loss and trans-generational trauma associated with

the impact of forced removal from families and /or country. The book is also intended for students working in courses in nursing, medical schools, social work, psychiatry, psychology and primary health care.

2011 saw a continuation and extension of the initial promotion, dissemination and evaluation of the book. Since commencing distribution of Working Together in August 2010 over 35,000 hard copies of the book have been widely distributed to a broad range of target audiences. The on-going feedback and evaluation from both the survey monkey feedback, and student, practitioner and stakeholder evaluations confirms that the book is an important and effective resource for a range of health, allied health practitioners and educators and other professionals and agencies supporting and working with Aboriginal and Torres Strait peoples in mental health and wellbeing.

Funders of the project: Office of Aboriginal and Torres Strait Islander Health

THE ABORIGINAL COLLABORATIVE COUNCIL ADVISING ON RESEARCH AND EVALUATION (ACCARE)

The Aboriginal Collaborative Council Advising on Research and Evaluation (ACCARE) was formed in 2008 to provide support and direction to Aboriginal research conducted through the Telethon Institute for Child Health Research (the Telethon Institute). ACCARE is a committee of the Institute Board advising on Aboriginal research.

The Council comprises a group of professional, passionate people committed to ensuring Aboriginal people and the wider Aboriginal community benefit from the research conducted through the Telethon Institute.

The goal and over-arching principles for the work of the Council is to ensure the facilitation, translation and application of research findings into policy and practice to improve health and wellbeing outcomes for Aboriginal families.

Staff and Students 2011

CENTRE FOR RESEARCH EXCELLENCE IN ABORIGINAL HEALTH AND WELLBEING (CREAHW)

RESEARCH STAFF

Dr Tamika Heiden, BSc, PhD

Tanya Jones, BA Psychology

Associate Professor Roz Walker, PhD, BA (Hons) Politics and Philosophy

Dr Michael Wright, PhD

KULUNGA RESEARCH NETWORK

MANAGER

Glenn Pearson, BA (Education), PhD candidate

RESEARCH STAFF

Nina Boydell, BA, Dip Ed

Rose Murray, Dip. Teaching (Primary), Graduate Cert. Indigenous Health Promotion

Dr Claire Scrine, PhD

Fred Stacey, BA

THE ABORIGINAL COLLABORATIVE COUNCIL ADVISING ON RESEARCH AND EVALUATION (ACCARE)

RESEARCH STAFF

Patricia Walsh

OTHER RESEARCH STAFF

Jacqueline-Anne Bradley

Jaxon Reibel

Awards

Dawn Bessarab, Richmond Fellowship Aboriginal & Torres Strait Islander Award, WA Social Worker of the Year Awards, 2011

Rhonda Marriott, Patron of the Nursing and Midwifery office WA – NAIDOC award, 2011

Sandra Eades, Centenary of International Women's Day – listed as one of 100 Aboriginal and Torres Strait Islander women who have achieved change in their communities, National Aboriginal and Torres Strait Islander Women's Alliance, 2011

External Committees

INTERNATIONAL

Roz Walker, Invited Valued Friend; Indigenous Research Network, Canada & USA (2011-)

NATIONAL

Roz Walker, Australian Research Association for Children and Youth (ARACY) (2006-);

Roz Walker, Association of Qualitative Research (AQR), Australia (2011-)

Roz Walker, National Advisory Committee for the Kimberley Empowerment Project (2011-)

LOCAL

Rose Murray, COAG Aboriginal Child Health Project Steering Group, (2010-)

Rose Murray, Aboriginal Health Action and Advisory Committee, (2010-)

Glenn Pearson, Health Consumer Council of Western Australia

Glenn Pearson, Curtin University Human Research Ethics Committee

Glenn Pearson, Telethon Institute for Child Health Research Consumer and Community Advisory Council

Glenn Pearson, Key Aboriginal Advisory Group, Strong Spirit Strong Future - Promoting Healthy Women and Pregnancies 2011

Roz Walker, Public Health Association (PHA) WA (2006-)

Roz Walker, Primary Health Care Research and Evaluation Network, WA (2006-)

Roz Walker, WA Australian Early Development Index Steering Committee (2010-)

Roz Walker, Steering Committee for the research project "Indigenous Meaning Making Through Narrative: Cultural Interpretations of Preventable Deaths in Children and Young People" (2009-)

Roz Walker, Pilbara Child and Youth Project (2009-)

Roz Walker, Pilbara Early Learning Alliance (2008-)

Invited Presentations

INTERNATIONAL

Roz Walker, From Marginalised to Empowered: Transformative Methods for Aboriginal Health and Wellbeing, 23rd Annual Native Health Research Conference, Niagara Falls, USA, July 2011

NATIONAL

Juli Coffin, We All Solid Port Augusta Youth Rally on bullying to kids and parents (Over 1000), Port Augusta, SA, November 2011

Roz Walker, Exploring Cultural Competence, Royal Australian and New Zealand Council of Obstetricians and Gynaecologists (RANZCOG) Indigenous Women's Health Meeting - Cairns - 3 - 5 June 2011

Roz Walker, Starting on Track: Addressing maternal and child health outcomes in the Western Desert, AIATSIS National Indigenous Studies Conference 2011 - 'Young and Old: Connecting Generations' 19-22 September 2011, Canberra

Roz Walker, Developing a community-led empowerment leadership and healing program in the Kimberley, AIATSIS National Indigenous Studies Conference 2011 - 'Young and Old: Connecting Generations' 19-22 September 2011, Canberra

Roz Walker, Consulting with the Community to develop an innovative and culturally responsive Empowerment, Healing and Leadership program; Community Feedback Forum, Broome 24 October, 2011

LOCAL

Juli Coffin, Solid Kids and Cultural Security – Lecture Geraldton November 2011

Juli Coffin, Creating a Culturally Secure University - Notre Dame Fremantle, WA August 2011

Juli Coffin, Introduction to Cultural Security Notre Dame Fremantle, WA May 2011

Juli Coffin, Cultural Security for the Midwest Murchison Health Sector Yamaji Forum, Office of

Health Department, Geraldton, WA May 2011

Rose Murray, Kicked to the Curb: Examining the critical factors in Aboriginal non-smoking, WA State Cancer Conference, Perth, 24 March, 2011

Glenn Pearson, Do You See What I See? Environmental Health Australia 66th Annual Western Australian, Environmental Health Australia (WA) State Conference Environmental Health: Imagine Life Without Us. South Perth 28th- 30th March 2012

Clair Scrine, Developing an empowerment, healing and leadership program in the Kimberly. Suicide Prevention in Aboriginal Communities. Perth, 14 September, 2011

Roz Walker, Aboriginal women's health and wellbeing, School of Nursing and Midwifery, Murdoch, University Peel Campus, Mandurah, WA October 2011

Roz Walker, Aboriginal young people health and wellbeing, School of Nursing and Midwifery, Murdoch, University Peel Campus, Mandurah, WA October 2011

Roz Walker, Research with Aboriginal Families, Indigenous Studies, Kulbardi, Murdoch University, Murdoch, WA, August 2011

Roz Walker, Lectures and workshops on cultural safety and cultural competence. Graduate Social Work Program, University of Western Australia, July 2011

Roz Walker, Lectures and workshops, Working towards cultural safety and cultural competence – principles and practice. State-wide Mental Health Graduate Registered Nurse Program, Education & Research Centre – Nursing North Metropolitan Area Service - Mental Health Shaw House, Graylands Hospital, May & September, 2011

Roz Walker, Guest Lecture, Aboriginal young people and Aboriginal women's health. School of Nursing and Midwifery, Murdoch University Peel Campus, September 2011

Roz Walker, Guest Lecture, Research with Aboriginal Families, Indigenous Studies, Kulbardi Murdoch University, October 2011

Active collaborations

Leslie L. Randall, RN, MPH Nez Perce Tribal member, Native American Health Research Network, to explore future collaborations between the CRE in Aboriginal Health and Wellbeing and the Indigenous Research Network (2011-); David Hendrix, Belgium Collaboration on Aboriginal traditional medicines to prevent scabies among Aboriginal families in remote communities – Scabies is a preventative but neglected tropical disease with a raft of adverse, long term outcomes (2011-)

BIOSTATISTICS, BIOINFORMATICS AND DATA SERVICES

Overview

Gone are the days when conducting one experiment meant obtaining one result. Modern science often involves single experiments generating millions of results, which need to be analysed alongside the wealth of data held in public databases. We have reached the point where the majority of scientific research projects simply cannot succeed without the intervention of advanced computing and statistical analysis. With the number of our researchers growing and an ever increasing reliance on the computational analysis of rapidly increasing research data sizes, both Bioinformatics and Biostatistics are becoming ever more important to the Institute. This Division encompasses both these closely linked disciplines.

Bioinformatics is a cutting edge research field that uses computing technology, mathematics and statistics to answer biological research questions. This year there has been a primary focus on the analysis of Next Generation Sequencing both at the transcriptome (RNA-Seq) and genome (Genome-Seq) levels. In addition we have created a platform for the simultaneous analysis of epidemiological data housed at multiple sites. Details of both these highlights are below.

The requirement for Biostatistics expertise cuts across all areas of research at TICHR and elsewhere. The aim of statistical analysis is to aid in the interpretation of complex numerical data which abounds in medical, health, and biological research. While many research groups at TICHR employ their own research statisticians and analysts, a common enthusiasm to share common problems as well as expertise, ensures that all biostatisticians at TICHR regularly meet to share and exchange ideas and problems, for mutual encouragement and stimulation.

The Data Services group provides specialised research support services to researchers and research groups at TICHR, in the areas of: data management, databases, and computer programming. A large proportion of the group's work involves developing 'database applications' (computer software) in 2 key areas. One is the collection of data for TICHR studies using questionnaires or data entry applications. The other area is research project management software for keeping track of study participants and their interactions with a research study.

During 2011, with strong encouragement from our chief research partners, all areas of the Division moved towards providing active collaboration and research support to the whole child health 'campus', TICHR, SPACH, and PMH research.

Bioinformatics

FUSIONFINDER

Richard Francis (TICHR), Katherine Thompson-Wicking (TICHR), Kim Carter (TICHR), Denise Anderson (TICHR), Ursula Kees (TICHR), Alex Beesley (TICHR)

The hallmarks of many cancers (including leukaemias and solid tumours) are chromosomal translocations that may lead to the occurrence of gene fusions, whereby two normally separated genes are brought into close proximity and activated as a single gene. This activation often results in an abnormal protein product, which can have oncogenic (cancer causing) properties. The importance of detecting gene fusions in cancer lies in the fact that as only cancerous cells contain these abnormal products they make ideal drug targets.

Recently, there has been a significant advancement in our ability to identify all products that are being activated within a cell at a single point in time. This collection of products is known as a cell's transcriptome. Using Next Generation Sequencing techniques at the transcriptome level (called RNA-Seq) we can now verify known and discover novel activated gene fusions. Trawling through the hundreds of millions of data points this technology produces to discover the 10-100 or so that point to the existence of a gene fusion is a considerable task, which is essential in order to direct the focus of downstream lab work.

We have written FusionFinder which is designed to automate the discovery of candidate gene fusion partners from RNA-Seq data. To date FusionFinder has been applied to a number of datasets both from within the institute and obtained elsewhere. These analyses have confirmed known gene fusions and detected additional previously unreported novel fusion genes, which have been confirmed experimentally and will shortly be published. FusionFinder is made freely available for non-commercial use and can be downloaded from the project website.

The study was funded by the WA State Government Centres of Excellence Program and the Children's Leukaemia and Cancer Research Foundation, Perth.

iCARE VIRTUAL DATASET INFRASTRUCTURE

Kim Carter, Richard Francis, and the iCARE Consortium

Research studies exploring the determinants of disease often require increased power to detect small effects. Obtaining sufficient sample sizes can be achieved through the pooling of datasets, although these are invariably in disparate locations. Coupled with this, ethico-legal and data-ownership issues may prevent the pooling of datasets or permanent data transfer across international borders. Methods that facilitate the sharing of research data that are both sympathetic with ethico-legal issues and enable more flexible and detailed statistical analyses are required to overcome this problem.

We have created a computational infrastructure that implements database federation techniques to provide researchers with simultaneous analytical access to datasets housed in disparate locations without the need for permanent pooling. The application is currently in use by the International Collaboration for Autism Registry Epidemiology (iCARE) who are analysing datasets from across Europe and Australia to

determine Autism risk factors and trends. Our platform is accessed and controlled via a secure project management and analysis web-interface we have created to facilitate querying of the federated research datasets. We are currently preparing a manuscript for publication, as well as preparing a generic version of the software for public release to the research community.

This work was funded by Autism Speaks (US).

TOXICITY EVIDENCE INTEGRATION

Alison Anderson (TICHR & UWA), Kim Carter (TICHR), Denise Anderson, Michael Wise (UWA)

Over the past decade evidence has accumulated that environmental contaminants are causing a range of adverse health outcomes. The aim of this PhD and research project is to explore how *in silico* bioinformatics approaches can help to reveal new relationships in toxicogenomics data by intelligently integrating toxicology, gene expression, and epigenetic and other 'omics platforms.

This work was supported by a William and Marlene Schrader Postgraduate Scholarship awarded by the William and Marlene Schrader Trust (through UWA).

DEVELOPING RISK MODELS FOR PREDICTING CHILDHOOD ASTHMA USING LINKED HEALTH DATA

Kim Carter (TICHR), Max Bulsara (Notre Dame), Peter Franklin (UWA), Monique Robinson (TICHR), Steve Stick (TICHR & PMH), Nick de Klerk (TICHR), Grant Smith (TICHR), Steve Ball (TICHR)

Asthma is the most common chronic illness in Australian children, and over half of all asthma-related hospitalisations are for children under 15. Research suggests that environmental and lifestyle factors play an important part in increasing the risk of developing asthma. Western Australia (WA) has internationally unique capacity to link population-based health data on individuals who have lived in the state over the past 4 decades. By combining existing health survey data and state health data with geographical and environmental data, we have a powerful resource for investigating factors influencing the development of childhood asthma and its epidemiology, without the need for conducting new surveys or expensive cohort studies. We are examining factors that contribute to childhood asthma risk in terms of psychosocial life stress, perinatal and family characteristics, sociodemographics and spatio-temporal influences using state of the art biostatistical and geospatial methods.

HOSPITALISATION, INFECTION, AND HEART DISEASE

Kim Carter (TICHR), David Burgner (MCRI), Matthew Cooper (TICHR), Nick de Klerk (TICHR), Peter Thompson (UWA), Fiona Stanley (TICHR), Hannah Moore (TICHR).

Cardiovascular disease is a major worldwide health and economic burden. Atherosclerosis (hardening and narrowing of the arteries) causes heart attacks, strokes, and peripheral vascular disease. Atherosclerosis is a chronic inflammatory process, with subclinical inflammation leading to vascular damage. There is mounting evidence that childhood infection may play a role in the initiation, progression or acute presentation of atherosclerosis which becomes clinically apparent in later life. We are investigating the relationship between severe infection in childhood and atherosclerosis in later life using the internationally unique linkable population-level health databases available in Western Australia.

This study is supported by a University of Western Australia, Research Development Award.

microRNA REGULATION IN BRAIN TUMOURS

Laura Genovesi (TICHR), Peter Dallas (TICHR), Kim Carter (TICHR), Keith Giles (WAIMR and UWA), Nick Gottardo (TICHR and PMH).

Medulloblastoma (MB) is the most common malignant brain tumours of childhood. Many children with these tumours remain incurable and survivors are often left with devastating long-term side effects.

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

We have analysed the expression levels of a panel of miRNAs in MB specimens and neural stem cells (NSCs) using qRT-PCR in a low-density array format, and have integrated these data with gene expression microarrays. We anticipate that ongoing research based on these data will rationalise our understanding of the fundamental molecular mechanisms that initiate and maintain the brain tumour phenotype

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

Biostatistics

Members of the Division collaborated closely with most research groups at TICHR, in particular:

Denise Anderson:

Major study involvement in(i) was involved in a number of Genome Wide Association Studies (GWAS) which aim to detect associations between genetic variants and human diseases or traits of interest. Some of the examples of the diseases and traits studied include asthma, type 2 diabetes, body mass index (BMI) and immune response. GWAS are a powerful tool to help unravel the multiple genes involved in a complex disease such as asthma.

(ii) was also involved in microarray gene expression studies which is a technology that enables measurement of genome wide gene expression. Gene expression can then be compared between groups of interest (e.g. normal patients versus cancer patients) to identify genes with altered expression that may play a role in the disease process. Groups of genes with altered expression are also analysed

to determine if they act together in a biological pathway which further helps to elucidate the disease process.

Matt Cooper:

Major study involveement in:

(i) Epidemiology of Epilepsy: Intrauterine growth historically been measured using crude methods of child weight distribution based on gestational age. Using the Proportion of Optimal Birth Weight (POBW), as calculated by a method derived at TICHR in 2005, we were able to investigate the association of intrauterine growth on the incidence of epilepsy in children. Results from this study show that children with both low and high POBW are at a higher risk of developing epilepsy during childhood compared to those who showed appropriate intrauterine growth. This finding is of interest to neurologists investigating the pathways that lead to the development of epilepsy by suggesting areas of the brain affecting during intrauterine growth may be involved.

(ii) Genotype Misclassification: When applying Whole Genome Amplification (WGA) there are a number of factors that can affect the quality of a sample, leading to incorrectly called genotypes (misclassification). A statistical method, applied in R, was created to correct for this misclassification when the misclassification rates can be quantified through comparison, using say a subset of data, between WGA genotypes and another method no misclassification. This correction method showed good performance in correcting model estimates over a range of different misclassification rates and sample sizes.

Peter Jacoby:

Major study involvement in:

(i) Continuing analysis of data from infectious disease studies including the Kalgoorlie Otitis Media research project and the Papua New Guinea neonatal pneumococcal conjugate vaccine trial.

(ii) Analysis of data from the WA influenza vaccine effectiveness study.

(iii) Methodological research involving simulations to evaluate the relative performance of different vaccine effectiveness observational study designs.

(iv) Collaboration with spatial epidemiologist (Steve Ball) to develop techniques for investigating geographical variation of disease incidence in WA. These techniques have been applied to an analysis of the role of socioeconomic disadvantage in explaining spatial variation in the prevalence of fetal growth-restricted births within metropolitan Perth.

(v) Investigation of the relationship between prenatal androgens measured in cord blood and subsequent mental health indicators using Raine study data.

(vi) Statistical support for other studies involving mental health outcomes in Raine study children including the association with prenatal stress (with Monique Robinson), maternal overweight (also with Monique) and parental work patterns (with Sarah Johnson).

(vii) Statistical support for a variety of studies conducted by Helen Leonard's team involving health and social outcomes for children with Rett syndrome and Down syndrome.

Nick de Klerk:

Major study involvement in:

(i) The Western Australian Twin Register as Director continuing with ongoing data collection and joining in data collection with the Australian Twin Register and joining the worldwide twin register consortium, Intrepid.

(ii) Continuing in a supervisory role for the Developmental Pathways Project.

(iii) Continuing in a supervisory role for the Raine Study, on the Executive Committee, Management Committee, and on the paper submission oversight and statistical advisory groups. Continued work with the mental health, diet and cardiovascular groups.

(iv) Continued collaboration with the Childhood Cancer Epidemiology Group in studies of ALL, CBT, and DNA damage.

(v) Continued collaboration with the cystic fibrosis group, in particular on the AREST-CF and COMBAT-CF studies.

(vi) working as part of the Epidemiology NHMRC Program Grant in particular on intellectual disability and autism, as well as input into the TICHR part of the CRC on Spatial Information, coordinated by Steve Ball.

(vii) Continued collaboration with the Occupational Respiratory Epidemiology group at UWA School of Population Health in: studies of environmental and occupational exposure to asbestos at Wittenoom and in Aboriginal communities (with James Cook University); GWAS for malignant mesothelioma; respiratory effects of silica exposure; studies of respiratory disease in the aluminium industry (with WAIMR and Monash University).

Data Services

Highlights and significant achievements for the group in 2011 include -:

Developing a database management system to be used by the 'WA Autism Register' to store and manage data in that register.

Creation of online surveys for collection of data relating to flu vaccinations as part of a project called the WA Influenza Vaccine Effectiveness Study (WAIVE).

Development of a project management system for the study: 'Pregnancy Investigation of Siblings and Mothers (PRISM)'. A longitudinal study aimed at identifying biomarkers for autism in-utero and in the early post-natal period.

The development of an online data collection questionnaire used to collect data for the 'Breathing for Life' study. This study is investigating breathing and airway problems in children and adults with Cerebral Palsy.

Re-development of a legacy 'Diabetes Patient Management System' used by the PMH Diabetes group to store clinical information on children with diabetes who are enrolled in

diabetes clinics. Data from this system is used for a variety of research collaborations of which TICHR is a research partner.

Staff and Students

HEAD OF DIVISION

First Name followed by surname followed by abbreviated qualifications followed by current positions. See example below.

Nicholas de Klerk, PhD.

Head of Bioinformatics and Biostatistics

Winthrop Research Professor, University of Western Australia

RESEARCH STAFF

Richard Francis, MSc.

Kim Carter, PhD.

Denise Anderson, BSc.

Marty Firth, BSc(Hons).

Phyllis Alessandri.

Michelle de Klerk.

Peter Cosgrove. BSc.

Girard Good.

Hoan Nguyen.

AFFILIATED STAFF

(funded from separate research grants but contributing to campus-wide biostatistics and bioinformatics collaboration and support)

Peter Jacoby, MSc.

Matt Cooper, BSc.

Patrick FitzGerald, PhD.

Amanda Langridge, PhD.

Guicheng Zhang, PhD.

POSTGRADUATE STUDENTS

Nick de Klerk co-supervised the following PhD students at UWA:

M-A Measey: "The epidemiology of unexplained fetal death in Western Australia" (submitted 2011); K Ayonrinde; L Mott; R Francis; M Jokic; S Fehr.

Awards

R Francis, Highly Commended for Excellence and Commitment to Research

K Carter, Highly Commended for Excellence and Commitment to Research

External Committees

NATIONAL

Nick de Klerk: NHMRC Academy

Nick de Klerk: Australian Working Group developing Radiation Protection Standard for Exposure to ELF

LOCAL

Kim Carter, Western Australian Data Linkage Network (2011-)

Kim Carter, Australian Society for Medical Research, WA Committee (2006 -)

Kim Carter, WA Deep Sequencer Users Group (2011-)

Kim Carter, WA Next-Generation Sequencing User Group (2011-)

Amanda Langridge: Scientific Advisory Sub-Committee, PMH Ethics Committee

Nick de Klerk: Clinical Drug Trial Committee, Sir Charles Gairdner Hospital

Nick de Klerk: Mesothelioma Committee of Western Australia - co-ordinating the Western Australian Mesothelioma Register

Nick de Klerk: Busselton Population Medical Research Institute Inc, Board & Research Committee.

Nick de Klerk: Western Australian Medical Radiation and Cancer Working Party

Invited Presentations

First name, surname followed by presentation title, conference/meeting name, city and date. See example below.

Richard Francis. "Building the iCARE Web-based Analysis Portal", The International Meeting for Autism Research (IMFAR), San Diego, CA, USA, May 2011.

Kim Carter. "A bioinformatics infrastructure for creating virtual pooled research datasets: Application to autism research". Asia Pacific Autism Conference, September 2011, Perth

Kim Carter & Richard Francis "Sophisticated techniques for sharing and analysing research data". Invited Speaker, Australian Research Alliance for Children and Youth (ARACY) Data Sharing and Harmonisation Workshop, Melbourne, October 2011

Nick de Klerk. Childhood leukaemia and exposure to ELF-EM fields: using epidemiological studies in guiding standard setting. Australian Radiation Protection Society, Annual Conference, Melbourne, 2011.

Nick de Klerk. Association of lung tissue content of different mineral fibre types with occurrence of malignant mesothelioma. 8th Perth Mesothelioma Group Symposium, Perth, 2011.

Nick de Klerk. Association of lung tissue content of different mineral fibre types with occurrence of malignant mesothelioma. EPICOH , Oxford, 2011.

Nick de Klerk. Some non-technical aspects of data integration – consumer and community support and engagement. SHIP , St Andrews, 2011.

Peter Jacoby. "Modelling the effect of crowding on carriage of otitis media bacteria". Australian Epidemiological Association Conference, Perth, September 2011

ACTIVE collaborations

Professor Paul Burton, University of Leicester, United Kingdom

Associate Professor David Burgner, Murdoch Children's Research Institute, Victoria, Australia

Dr Diana Schendel, Centres for Disease Control (US) & head of the International Collaboration for Autism Registry Epidemiology (collaboration of leading Autism researchers located at Karolinska Institute (Sweden), Aarhus University (Denmark), Turku University (Finland), Kings College London, the Norwegian Institute of Public Health, Columbia University (US), CDC (US) and TICHR)

Overview

The central research theme of this Division is the basis for resistance versus susceptibility to asthma, in particular we are seeking to elucidate the mechanisms that drive this disease are operative during its very early stages. Our long-term goal is to utilize this information to guide the development of preventative treatments for asthma for use in early childhood, before the disease consolidates into its persistent form. In addition, we have developed a specific focus on the mechanisms responsible for triggering acute severe asthma attacks in children with established asthma, in particular how virus infections harness allergic responses to aid them in escaping antimicrobial defences. We are also continuing our research in areas related to pediatric vaccines and immune enhancers, particularly those which increase resistance to respiratory infections. A unifying theme in this research stems from our earlier findings that risk for development of allergy, respiratory infections and asthma is determined primarily by factors that control the functional maturation of the immune system during early childhood. In particular we have shown that a variety of the cellular immune effector mechanisms which are suppressed *in utero* in order to protect the placenta from inflammatory damage are vital for protection against both infections and allergy during infancy, and the speed of their functional maturation during the preschool years is retarded in children from families with a history of allergic diseases. An important complementary stream of research in our Division involves animal model studies on immunoregulation of the cell populations responsible for triggering T-lymphocyte activation in the airway mucosa during the "late phase response" in asthma. The main focus of this aspect of our research is on interactions between T-regulatory cells and the network of airway mucosal Dendritic Cells that are responsible for immune surveillance in the respiratory tract. We are additionally expanding this experimental area to encompass viral infections and how these interact with and exploit allergic inflammatory mechanisms. In addition, we have developed a network of national and international collaborators to translate some of the key findings from this research, into clinical settings.

Aetiology and pathogenesis of atopy and asthma

MODULATION OF IGE-ASSOCIATED RISK FOR WHEEZE VIA ALLERGEN-SPECIFIC IGG

P.G. Holt, A. Custovic[1], S. Ahlstedt[2], P.D. Sly[3]

[1]The University of Manchester Academic Health Science Centre, UK;

[2]Centre for Allergy Research, Karolinska Institute, Stockholm, Sweden;

[3]Queensland Children's Medical Research Institute, University of Queensland

As part of a long term collaboration with colleagues in UK and Sweden, we have been studying the relationships between antibody responses to aeroallergens and risk for asthma-like wheezing symptoms amongst children of different ages and from different geographic locations. A major component of these studies has involved parallel analysis of IgE and IgG antibody subclass responses to major aeroallergens, comparing results obtained on large birth cohorts from Manchester and Perth. In our case this involved 1100 and 1400 serum samples respectively from subjects assessed in the 5yr and 14 year followups of the RAINE cohort, and these were compared with ~500 samples from the Manchester cohort. The study focused on responses to cat allergen, which is recognized as a strong trigger for respiratory allergies and asthma-like symptoms in both Australia and UK. As expected, univariate regression analysis demonstrated that risk for wheezing symptoms increased with serum IgE titres against the major cat allergen FelD1, in both populations. However, recent studies in other areas of allergy suggested to us that additional elements of the allergic response to cat may also be involved. In particular, studies from a number of centres on the use of immunotherapy to suppress IgE-associated allergy symptoms have suggested that the success of this treatment may be due in part to stimulation of production of allergen-specific IgG antibody from the IgG4 subclass, which binds circulating allergen and prevents it from reacting with IgE. We already had evidence that the immune response of allergic (and non allergic) children to natural (environmental) cat exposure also involved production of some IgG4 antibodies, and so we tested the theory that as per the situation in immunotherapy, naturally produced cat-specific IgG4 may reduce the allergy-promoting effects of IgE. We indeed demonstrated significant attenuation of cat-specific IgE-related wheeze by cat-specific IgG, but unexpectedly found that the type of IgG involved in this case was the more abundant IgG_1 subclass, in contrast to the IgG_4 which is active in the context of immunotherapy. Followup studies are in progress with colleagues in London to further investigate the mechanism(s) of this "blocking" effect, and to test the possibility that deliberate stimulation of allergen-specific IgG_1 production may be a valid target for development of new asthma treatments.

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

EARLY RESPIRATORY INFECTIONS AND DEVELOPMENT OF PERSISTENT ASTHMA: FEVER AS A MARKER OF RISK

M.M.H. Kusel, P.G. Holt, in collaboration with P.D. Sly[1] and S.L. Johnston[2]

[1]Queensland Children's Medical Research Institute, University of Queensland;

[2]Imperial College, London

During 2011 we completed the 10 year followup on the CAS birth cohort, encompassing a group of 147 children selected on the basis of high risk for asthma and allergy as defined by positive family history. The main aim of this prospective birth cohort study has been to collect detailed information concerning the respiratory infection history of these children throughout their first 5 years of life, and determine how this relates to their risk for development of asthma initially at age 5yrs, and in turn for asthma that persists into later childhood. As part of this study, collaborators initially in London and now in the

US and in Melbourne are using genomics-based techniques to identify the viral and bacterial microflora that was present in the airways of these children at the time of each infection, and we will factor this information into our ongoing analyses during 2012.
An important breakpoint in this study was reassessment of the relationship between the frequency and (most importantly) the intensity of infant lower respiratory infections (LRIs) and risk for asthma, focusing on outcomes beyond age 5yrs. In particular we wanted to reassess the relative impact of early LRIs that were associated with wheezing symptoms, which have traditionally been assumed to carry maximal risk for later asthma development, and to compare these with infections associated with febrile responses. Both wheeze and fever in association with infant LRI were equivalently strong markers of risk for asthma at age 5yrs. However, it is now recognized that a significant proportion of children carrying a physician diagnosis of asthma at the end of the preschool years in reality have a relatively benign form of wheeze due mainly to low airway caliber, which spontaneously resolves over the ensuing few years, revealing the truly "persistent" asthmatics. Of major interest in this context: we have now shown via the 10year outcome data in the CAS cohort that the impact of wheezy infections wanes over time and maximal risk for asthma that persists to age 10 is associated with infections that trigger febrile responses. This is suggestive of underlying hyperactivity of the inflammasome component of the host response to infection in affected children, and we are exploring this hypothesis in a new NHMRC-funded project (commencing 2012), focusing on cryobanked clinical material from the CAS children.

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

GENOME-WIDE ASSOCIATION AND LARGE-SCALE FOLLOW UP FOR IDENTIFICATION OF NEW GENETIC LOCI INFLUENCING LUNG FUNCTION

P.G. Holt in collaboration with C.E.Pennell[1], P.D.Sly[2] and the consortium detailed in *Nature Genetics* 2011:43(11):1082-90.

[1]School of Women's and Infants' Health, The University of Western Australia;

[2]Queensland Children's Medical Research Institute, University of Queensland.

Pulmonary function measures reflect respiratory health and are used in the diagnosis of a variety of pulmonary diseases. A large international consortium of researchers, which has included our group contributing data from the 14yr respiratory followup of the RAINE birth cohort, have pooled resources in order to mount a large scale genome wide association study to identify genetic variants which influence lung function. The group has tested genome-wide association with forced expiratory volume in 1 second and the ratio of forced expiratory volume in 1 second to forced vital capacity in 48,201 individuals of European ancestry with follow up of the top associations in up to an additional 46,411 individuals. New regions were identified showing association (combined $P < 5 \times 10{-}8$) with pulmonary function in or near MFAP2, TGFB2, HDAC4, RARB, MECOM (also known as EVI1), SPATA9, ARMC2, NCR3, ZKSCAN3, CDC123, C10orf11, LRP1, CCDC38, MMP15, CFDP1 and KCNE2. Identification of these 16 new loci may provide insight into the molecular mechanisms regulating pulmonary function and into molecular targets for future therapy to alleviate reduced lung function. We are proceeding with this collaboration on a number of fronts related to respiratory functions and susceptibility to asthma and related diseases.

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

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

D. Mok, K. Holt[1], M. Inouye[2], E.M. Hollams, B.J. Holt, M.M.H. Kusel, P.D. Sly[3], P.G. Holt

[1]Microbiology Department, University of Melbourne

[2]Department of Pathology, University of Melbourne

[3]Queensland Children's Medical Research Institute, University of Queensland.

Accumulating evidence suggests a potential role of bacterial infections in the pathogenesis of childhood asthma. This is particularly relevant within the first year of life, where we hypothesise that early colonisation of the airways with specific bacteria predisposes children towards development of asthma. We are testing this premise in the Childhood Asthma Study (CAS) birth cohort, which comprises children at high-risk for asthma and allergy due to parental history of allergy. Post-nasal aspirate samples were collected and cryobanked from CAS participants both at regular follow-up appointments and at times of respiratory infection up to age 5 years. A pilot study was initiated in collaboration with Drs Kathryn Holt and Michael Inouye, to assess the use of nasopharyngeal aspirate samples to identify whole bacterial communities within an individual's upper respiratory tract, using cutting-edge metagenomics techniques. We have utilized post-nasal aspirates obtained from a panel of 3-6 month old infants, collected at a routine follow-up without respiratory infection ("controls"). Sequencing by the Roche 454 GS FLX Titanium genome sequencer detected ~200 bacterial genera. Significantly, the abundance of *S. pneumoniae* positively associated with wheeze at 5 years of age. Abundance of *S. pneumoniae* also associated with colonisation by genera *Moraxella*, *Haemophilus*, *Porphorymonas*, *Prevotella*, *Gemella*, *Lactobacillus*, *Veillonella*, *Fusobacterium*, *Neisseria* and lower odds for *Acinetobacter* or *Methylobacterium*. A small subset of these samples was re-sequenced by Ion Torrent, for validation of the bacterial reads as determined by 454 sequencing. Analysis of these reads is currently ongoing, before proceeding to the next phase of the project, which is to examine samples in the cohort collected at the time of a respiratory infection, for bacterial profiling by 454

sequencing. Changes in bacterial colonisation will then be tracked back to the controls to determine the relationships between the composition of upper airways bacterial flora and risk for asthma development in childhood.

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

PREVENTION OF VIRUS-ASSOCIATED ASTHMA EXACERBATIONS IN ATOPIC CHILDREN

P.G. Holt, A. Bosco, D.H. Strickland in collaboration with P.D. Sly[1], P.N. Lesouef[2], and M. Tang[3].

[1]Queensland Children's Medical Research Institute, University of Queensland;

[2]Dept of Pediatrics, University of WA;

[3]Murdoch Childrens Research Institute, University of Melbourne.

Ongoing studies in the Division point to an important role for atopy, acting in concert with viral infection, in triggering acute severe asthma exacerbations in children. In particular, we have demonstrated that upregulation of high affinity IgE receptors (FcER1a) on the bone marrow derived precursors of airway mucosal dendritic cells (DC), triggered by stimuli released during the host response to respiratory viral infection, provides a potential mechanism for the recruitment of atopic inflammatory pathways into the overall antiviral response in airway tissues. In particular, arming airway DC with FcER1a may lead to IgE binding to the DC surface which can be used to enhance their efficiency in allergen sampling, in turn leading to amplified presentation to and ensuing activation of pro-inflammatory Th2 effector cells; if this occurs at tissue sites already inflamed as a result of viral infection and associated immune responses, the result may be a self-sustaining inflammatory cascade. The results of epidemiological studies from a number of groups on patterns of expression of severe asthma exacerbations during the "common cold season" in atopic children are consistent with such a mechanism. If this is explanation is correct, it follows that "blocking out" IgE during the virus season may prevent the triggering of this amplification loop, and help to maintain levels of airways inflammation ensuing from viral infection below the threshold required for severe asthma exacerbation. The collaborators in this project have secured NHMRC funding to test this hypothesis via treatment of high risk atopic children with anti-IgE (Xolair) over the winters of 2012/13.

This work is funded by the National Health and Medical Research Council of Australia with drug support from Novartis (Switzerland).

IDENTIFICATION OF THE GENE NETWORKS THAT UNDERPIN INFLAMMATORY PROCESSES IN ASTHMA

A. Jones, P.G. Holt, A. Bosco

It is well known that viral infections and exposure to allergens can cause asthma, but our knowledge of the molecular processes involved is incomplete. We are currently utilizing molecular profiling technologies and data analysis algorithms to generate computational models of the gene networks that cause asthma symptoms in humans in vivo. A major focus of this work is to characterize the role of IRF7 in regulation of the gene networks that underpin viral asthma exacerbations in children. In parallel we are also developing novel humanized mouse models of asthma to determine how inflammatory gene networks damage the airways and impact on lung function.

This work is funded by the University of Western Australia.

Pediatric Vaccine Studies

DEVELOPMENT OF GENOMICS-BASED APPROACHES TO ASSESSING THE SAFETY OF PEDIATRIC VACCINES

P.G. Holt, A. Bosco, K.L. McKenna, O. White, A.H.J. van den Biggelar, E.M. Hollams in collaboration with P. Richmond[1]

[1]School of Pediatrics and Child Health, UWA

Immune responses to vaccines in infants and young children are typically Th2-biased, giving rise to concerns regarding potential atopy-like side effects exemplified by the injection-site reactions observed in a subset of atopic children immunized with the diptheria/acellular pertussis/tetanus (DTaP) vaccine under the original infant vaccination schedule. Associated theoretical concerns also exist regarding potential antagonism or deviation of Th1-mediated sterilising immunity. Conventional immunological methodology has limited capacity to effectively address these problems because of the inherent complexity of the immune responses involved. A number of groups have recently sought to develop unbiased systems biology approaches to investigate these issues. We have recently published the results of one such study from our group involving attempts to elucidate superficially similar Th2-associated responses to paediatric vaccines and allergens, and to differentiate between them via gene coexpression network analysis. We have demonstrated that in immune responses to the DTaP and pneumococcal polysaccharide conjugate vaccines, potentially antagonistic Th1-/IFN-associated and Th2-associated gene networks coexist in an apparent state of dynamic equilibrium, whereas in Th2-dominant allergen-specific responses of atopics the Th1 and IFN networks are respectively disrupted and downregulated. Capacity to detect and interpret these covert differences between responses to vaccines and allergens relies on the use of sophisticated algorithms that underpin coexpression network analysis, which identify genes that function co-ordinately in complex pathways. This methodology has significant potential to identify covert interactions between inflammatory pathways triggered by vaccination, and as such may be developed further into a useful tool to aid in prediction of vaccine safety/efficacy.

This work is funded by the National Health and Medical Research Council of Australia and Wellcome Trust (UK).

PNEUMOCOCCAL CONJUGATE VACCINATION AT BIRTH IN A THIRD WORLD SETTING: NO

EVIDENCE FOR NEONATAL T-CELL TOLERANCE

A.H.J. van den Biggelaar, W. Pomat[1], A. Bosco, S. Phuanukoonnon1, C.J. Devitt, M.A. Nadal-Sims, P.M. Siba1, P.C. Richmond[2], D. Lehmann, P.G. Holt

[1]Papua New Guinea Institute of Medical Research

[2]School of Paediatrics and Child Health, University of Western Australia, Princess Margaret Hospital for Children

Concerns about the risk of inducing immune deviation-associated "neonatal tolerance" as described in mice have restricted the widespread adoption of neonatal vaccination. The aim of this study was to demonstrate the immunological feasibility of neonatal pneumococcal conjugate vaccination (PCV) which could potentially protect the most vulnerable age group in high-risk human populations in 3rd world settings against severe pneumococcal disease and mortality. In Papua New Guinea, 313 newborns were randomised to be vaccinated with the 7-valent PCV (7vPCV) at birth, 1 and 2 months (neonatal group, , n = 104), at 1, 2 and 3 months of age (infant group, n = 105), or not to receive 7vPCV (control group, n = 109). T-cell and pneumococcal serotype specific IgG antibody titers were assessed at 3 and 9 months of age and children were monitored for disease to age 18 months. Despite transient Th2 polarisation of memory responses to the PCV-carrier protein at 3 months, neonatal vaccinees manifested protective levels of pneumococcal serotype-specific IgG antibody at this age, and by 9 months displayed balanced and stable Th1-polarised memory responses accompanied by antibody titres that were equivalent to subjects vaccinated later in infancy. PCV vaccination at birth is safe and not associated with immunological tolerance. Neonatal immunisation schedules should therefore be considered in high-risk areas where this may result in improved vaccine coverage and the earliest possible protection against pneumococcal disease and death.

NEONATAL ANTIGEN PRESENTING CELL FUNCTION IN CHILDREN FROM 1ST VERSUS 3RD WORLD ENVIRONMENTS

J.G. Lisciandro[1], S.L. Prescott[1], M. Nadal-Sims, C.J. Devitt, P.C. Richmond1, W. Pomat[2], P.M. Siba[2], P.G. Holt, D.H. Strickland, A.H.J. van den Biggelaar^

[1]School of Paediatrics and Child Health, University of Western Australia, Perth, Australia

[2]Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea

^ Current affiliation: Crucell, Innovation & Discovery Lab, Archimedesweg 4-6, 2333 CN, The Netherlands

There is increasing interest in the possibility that there may be developmental differences in immune functions between infants born in 1st and 3rd world environments, which in turn influence their responses to early vaccination. With this in mind, as part of our studies on responses to the PCV vaccine in Papua New Guinea (PNG) infants, we have been investigating the functions of neonatal antigen presenting cells (APC) in children born in PNG compared to those born in Australia (AUS). These studies involve collecting cord blood mononuclear cells (CBMC) from PNG and AUS newborns and comparing both APC and T cell phenotype and function. AUS cord naïve T cells ($CD4^+CD25^-CD127^+$) showed an enhanced and more rapid proliferative response in an autologous APC-dependent culture system, a result of differences in neonatal APC rather than T-cell function. This included an increased capacity to process antigen and to up-regulate activation markers following stimulation. In contrast, resting PNG APC exhibited higher baseline levels of activation and inhibitory markers, and were less or non-responsive to stimulation *in vitro*. This study supports the hypothesis that prenatal environments can influence the developing immune system *in utero*, in particular children born under modern environmental conditions exhibit increased APC reactivity at birth compared to children born under 3rd world environmental conditions. We speculate that the functionally more quiescent nature of PNG neonatal APC may represent an adaptation to the more robust 3rd world microbial environment in which relatively high-level exposure of newborns to proinflammatory microbial stimuli represents the norm; the significance of these findings in relation to vaccine responsiveness in early life remains to be established.

Animal Model Studies

DETERMINING THE FACTORS THAT GOVERN RESOLUTION OF ALLERGIC AIRWAYS INFLAMMATION

D.H. Strickland, J.A. Thomas, A.N. Larcombe, P.G. Holt.

This study aims to map the central mechanisms that underpin expression of atopic asthma at the target tissue level, and hence regulation of the maintenance of "normal" function in the airways. In humans, sensitization to aeroallergen(s) is one of the major risk factors predictive of development of chronic asthma. We have developed a unique rat model featuring two inbred rat strains closely approximating human "high risk for allergy - HR" and "low risk for allergy LR" phenotypes. We have established that in sensitized LR rats, continued aeroallergen challenge involves the induction of a regulatory network (involving interactions between specific cell types within the airway microenvironment) that operates to efficiently control the intensity and duration of allergic airways responses. In contrast, sensitized HR animals mount exaggerated uncontrolled airway responses to repeated aerosol challenge, resulting in a more persistent and severe form of inflammatory disease with continuing airways inflammation and hyperresponsiveness (both hallmarks of the human chronic atopic asthmatic response). Our studies have demonstrated that in the airway mucosa of HR rats there is an association between the development of persistent AHR and reduced

number and function of cells capable of regulating the inflammatory airways response. Moreover, we have also demonstrated a series of abnormalities in the functions of other major cellular players associated with both the development and expression of disease, namely airway mucosal dendritic cells (AMDC) and T helper cells. Furthermore, these abnormalities are restricted to respiratory tissues. Our findings suggest that "site specific" factor(s) related to the airway mucosa microenvironment may ultimately determine whether allergic individuals mount a chronic asthmatic response to aerosol allergen exposure. Most importantly, we have shown that "correcting" for the deficiency that we have identified in HR animals can reverse ongoing disease. The concept of "site specific failure of regulation" underpinning these experimental model studies, if it can be validated and elucidated mechanistically, offers exciting new possibilities for drug development for asthma treatment, and this represents the long-term aim of our research program.

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

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

D.H. Strickland, V. Fear, J.A. Thomas. P.G. Holt.

We are expanding our asthma research to encompass how viral infections interact with and exploit allergic inflammatory mechanisms. Our initial phase has been to establish the viral infection models in our rats strains. We are using a Rhinovirus (RV) adapted to infect rats (mengovirus) to best compliment the findings in humans that have shown strong associations between RV infection and acute asthma exacerbation in children. We have documented the response to viral infection following a time course post infection day in the HR and LR rat strains, including viral titres in bronchoalveolar lavage (BAL) fluid and lung homogenates, airways inflammatory response and cytokine response in BAL fluid. We are currently finalising the assessment of T cell and DC population responses following the same time course as above post infection in the rat strains. Once baseline infection data is completed work will progress to overlaying viral infection on sensitized/ challenged rats to enhance our current understanding of how viral infection markedly amplifies local Th2 responses to aeroallergen challenge in the airway mucosa of sensitised rats, increasing the intensity of acute inflammation and the duration of ensuing airways hyperresponsiveness (AHR).

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

THE ROLE OF THE INTEGRIN CD103 IN DEVELOPMENT OF AIRWAYS HYPERRESPONSIVENESS

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

In humans, CD103 is expressed on the majority of $CD4^+$ and $CD8^+$ T cells in gut, compared to minor numbers of T cells in peripheral blood. CD103 expression has been characterized in mice in great detail, and similarly to human the majority of intraepithelial T cells in the gut are $CD103^+$. In mice, it has been reported that a large proportion of mucosal T cells are $CD103^+$, compared to a small proportion of splenic or blood T cells. CD103 is also expressed on some dendritic cell (DC) subpopulations and these have been associated with T cell immunity at barrier sites such as the intestine and skin. In the respiratory mucosa, it is known that CD103 and CD11b (reciprocally) expressing AMDC subsets exist, however we currently have little knowledge of their specific role in the cycle of inhaled antigen capture, processing and delivery to airway draining lymph nodes (DLN) for presentation to T cells and induction of immune responses. To explore the role of CD103 on DC we are using CD103 knock-out (CD103KO) animals and our well-characterised model of experimental allergic airways inflammation. Our initial studies have demonstrated significant differences in the development of airways hyperresponsiveness (AHR) in CD103 KO compared to normal mice. Interestingly, whilst AHR responses were reduced, CD103 KO mice still developed airways inflammation characterised by eosinophil infiltration indicating that the mice had been sensitised to the allergen. These findings are novel and raise the question of how this response is being mediated. Initial studies suggest that T cell recruitment into airways is unchanged in CD103KO mice, thus not the limiting factor in AHR development in this model. However, naïve T cell numbers in draining lymph nodes were increased in CD103 KO mice suggesting that T cell retention in DLN may play a role. Work is continuing on characterising this response, with focus on further characterising the inflammatory response in CD103 KO mice in terms of cytokine production and other potential regulatory T cell responses. Additionally as CD103 is associated with binding to epithelial cells, we are in the process of identifying the precise location of DC subsets within the lung and airways of CD103KO mice. As location may be central to antigen capture this may potentially play a role in the ensuing immune response.

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

PULMONARY IMMUNE RESPONSE AND LUNG FUNCTION ALTERATION IN THE DEVELOPING LUNG SYSTEM AFTER EXPOSURE TO NANOPARTICLES

K.G. Schuepp, J.A. Thomas, G. Zosky, P.G. Holt, D.H. Strickland.

Nanoparticles offer promising new possibilities for diverse biomedical applications due to the unique physico-chemical properties that they possess. Currently, much attention is being focused internationally on providing rationale for use of nanotechnology in biomedical applications. One of the potential uses of nanoparticles is as delivery vehicles for lung-based vaccines for children. In this context it is known that exposure of children to larger particles, such as traffic-related pollutants, can have adverse effects on health. It is recognised that ambient air can contain significant levels of nanoparticles from many sources. However,

the potential effect of nanoparticle exposure, particularly in children, on later health outcome remains unclear. We hypothesize that following exposure to nanoparticles the responses of the developing respiratory tract will significantly differ from adult responses and have initiated a research program to investigate this. Our initial studies have been to determine baseline developmental data on the pulmonary immune system of mice, focusing on different cell populations that are known to play central roles in immunity, and comparing neonates to adults. This has been done for various tissues, including lung, airway mucosa, draining lymph nodes and bronchoalveolar washouts. Additionally we have also mapped lung function at various developmental ages from neonate to adult. Using bioengineered fluorochrome-labelled particles we have exposed neonatal and adult mice via the respiratory route to nanoparticles and are currently assessing the inflammatory changes induced in various respiratory tissues. To complement this data we are also determining the effect of nanoparticle exposure of various aged mice on lung function.

This work was funded by the Asthma Foundation of WA, and supported by the Friends of the Institute.

Staff and Students

HEAD OF DIVISION

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Mrs J.A. Thomas, BSc - Research Officer

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VISITING RESEARCH FELLOWS

Dr Karen Schuepp MD, University Children's Hospital, Bern, Switzerland.

External Committees

INTERNATIONAL

Patrick Holt. NIH Expert Committee on Immunotherapy.

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

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

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

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

Deborah Strickland. Asthma UK

Deborah Strickland. Netherlands Asthma Foundation.

NATIONAL

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

Deborah Strickland. Murdoch Vet and Biomedical School Grant Review Panel

PRESENTATIONS 2011

Patrick G. Holt

Plenary Speaker: Regulation of immunological homeostasis in the respiratory tract – ERS Lung Science Conference, Estoril, 2011.

Symposium Speaker: Preventing development of allergic diseases via oral mucosal immunotherapy – AAAAI Congress, San Francisco, 2011.

Symposium Speaker: Innate immunity, allergy, and asthma exacerbations – AAAAI Congress, San Francisco, 2011.

Keynote Plenary Speaker: Bridging the gap between innate and adaptive immunity in the lung – Keystone Symposium, Vancouver, 2011.

Symposium Speaker: Altered immune responses and asthma development – ATS Congress, Denver, 2011.

Symposium Speaker: Interactions between atopic and antimicrobial pathways in asthma pathogenesis – EAACI Congress, Istanbul, 2011.

Symposium Speaker: The role of airways

inflammation in development of persistent asthma during childhood: emerging targets for asthma prevention – 10th World Congress on Inflammation, Paris, 2011.

Symposium Speaker: Food and inhalant allergy - 2nd Saudi Allergy, Asthma and Clinical Immunology Symposium, Riyadh, 2011.

Symposium Speaker: The role of infections in asthma pathogenesis - 2nd Saudi Allergy, Asthma and Clinical Immunology Symposium, Riyadh, 2011.

Symposium Speaker: Primary and secondary prevention of allergy - 2nd Saudi Allergy, Asthma and Clinical Immunology Symposium, Riyadh, 2011.

Plenary Speaker: New perspectives on asthma – WAO Regional Congress, Dubai, 2011.

Workshop Presenter: Development of asthma – preventative strategies for use in children - NIH Workshop, Washington, 2011.

Plenary Speaker: Immune-infection interactions in the early development of allergy – PAAM Congress of EAACI, Barcelona, 2011.

Deborah H. Strickland

World Immune Regulation meeting, Davos, Switzerland; Speaker and session Chair and judge

Bern University Hospital, Davos, Switzerland

NATIONAL

ASMR; Session chair and judge

Child and Adolescent Health Research Symposium; Judge

Australian Society Immunology, Annual Meeting, Mucosal Special Interest group

Active collaborations

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

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

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

Adnan Custovic, University Hospital of South Manchester, UK

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

Mimi Tang, Royal Children's Hospital, Melbourne, Australia

Claus Bachert, Gabi Holtappels, UZG, Upper Airway Research Laboratory, Belgium

Hugh Sampson, Department of Pediatrics, Division of Allergy & Immunology, Mount Sanai 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

Charles Hardy, Monash University, Melbourne, Australia

Christophe von Garnier, Bern University Hospital, Bern Switzerland

CHILDREN'S LEUKAEMIA AND CANCER RESEARCH

Overview

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

The Division focuses on research into childhood leukaemia, brain tumours and a very rare disease in children, undifferentiated 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 microarray and sequencing technologies. Our experimental model systems, including a panel of established leukaemia and cancer cell lines, are ideal tools for testing potential new drugs for the treatment of patients.

Acute lymphoblastic leukaemia

INTERACTIONS BETWEEN ACUTE LYMPHOBLASTIC LEUKAEMIA AND BONE MARROW STROMAL CELLS INFLUENCE RESPONSE TO THERAPY

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

The cure rate for paediatric patients with B precursor acute lymphoblastic leukaemia (pre-B ALL) is steadily improving, however relapses do occur despite initial response to therapy. To identify links between drug resistance and gene deregulation we used oligonucleotide microarray technology and determined in 184 pre-B ALL specimens genes differentially expressed compared to normal $CD34^+$ specimens. We identified 20 signature genes including *CTGF*, *BMP-2*, *CXCR4* and *IL7R*, documented to regulate interactions in the bone marrow. We recorded remarkably similar levels of expression in three independent patient cohorts, and found distinct patterns in cytogenetically defined subgroups of pre-B ALL. The canonical pathways that were affected are involved in inter- and intra-cellular communication, regulating signaling within the microenvironment. We tested experimentally whether interaction with stromal cells conferred protection to four drugs used in current ALL therapy, and demonstrated that bone marrow stromal cells significantly influenced resistance to vincristine and cytosine arabinoside. Compounds designed to block the identified cellular interactions within the bone marrow microenvironment are expected to mobilise the leukaemic cells and make them more accessible to contemporary antileukaemic agents. The data provide novel insight into the pathobiology of ALL and indicate new therapeutic targets for patients with ALL.

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

ROLE OF MICROENVIRONMENT INTERACTIONS IN CHILDHOOD LEUKAEMIA

JE Wells, M Howlett, J Ford, AL Samuels, J Heng and UR Kees in collaboration with C Cole, Haematology-Oncology, Princess Margaret Hospital and DR Brigstock, Paediatric Surgery Research Laboratory, Children's Research Institute, Columbus, Ohio, USA.

In children with acute lymphoblastic leukaemia (ALL) the bone marrow microenvironment is the site of leukaemic cell proliferation. Recently, the surrounding bone marrow stromal cells have been shown to play a critical role in clinical outcome by affecting leukaemic cell survival and drug resistance. The mechanism by which this stromal protection takes place is unclear. To identify genes and pathways linked to the disease and drug resistance we performed transcriptional profiling of B precursor (pre-B) ALL compared to normal $CD34^+$ cells. We found that connective tissue growth factor (*CTGF*) was overexpressed in 75% of pre-B ALL specimens and showed a 19-fold up-regulation by qRT-PCR versus normal $CD34^+$ cells. Incubation of recombinant human *CTGF* with either a pre-B ALL cell line or a human bone marrow cell line (HS5) was examined to monitor effects on proliferation and adhesion. *CTGF* increased proliferation of bone marrow stromal cells yet did not alter the proliferation of pre-B ALL cells. Furthermore, *CTGF* acted on stromal cells to increase adhesion of pre-B ALL cells to the stroma. Microarray gene expression analysis of HS5 cells incubated with *CTGF* affected genes involved in cholesterol and fatty acid metabolism, extracellular matrix production, cell motility and cell cycle. This clear link between *CTGF* and interactions between pre-B ALL and microenvironment will be validated and further characterised in vitro through overexpression of *CTGF* in pre-B ALL cells using stable retroviral transfection. We hypothesise that secretion of *CTGF* initiates a cascade of events, contributing to leukaemogenesis and adhesion-mediated drug resistance. Delineating these events will lead to a better understanding of therapy resistance in children with ALL and strategies for overcoming resistance.

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

CPG ISLAND METHYLATION CORRELATES WITH CTGF GENE EXPRESSION IN PAEDIATRIC PRE-B ACUTE LYMPHOBLASTIC LEUKAEMIA

M Welch and UR Kees in collaboration with

WK Greene, Division of Health Science, Murdoch University, Perth.

Acute lymphoblastic leukaemia (ALL) is the most common form of childhood cancer, with precursor B-cell (pre-B ALL) comprising around 80 percent of ALL cases. Using microarray technology we compared the gene expression profile of pre-B ALL to normal CD34+ and $CD19^{+}$/IgM^{neg} cells. Many of the top ranked genes identified in this study are known to mediate cell-cell interactions. One of them, connective tissue growth factor (*CTGF*) has been implicated in the biology of several solid tumours. Four independent studies on B-lineage ALL in paediatric and adult patients showed that 75 percent of patients expressed *CTGF* at very high levels, and in our paediatric patient specimens *CTGF* was expressed over a wide range from 2.3 to 380-fold by array measurement. Immunoblotting confirmed secretion of *CTGF* in our panel of pre-B ALL cell lines and interestingly, novel variants of *CTGF* mRNA were identified in several *CTGF*-positive cell lines by RNA blotting and sequencing of RACE products. *CTGF* is not normally expressed in B cells or their progenitors and secretion of *CTGF* proteins may play a prominent role in ALL, leading to modified interactions with the microenvironment.

The present study focused on investigating the mechanism of *CTGF* gene deregulation by genetic and epigenetic mechanisms. Analysis of the *CTGF* locus by Southern blotting ruled out rearrangements disturbing the *CTGF* locus. A combination of bisulfite sequencing and methylation-specific PCR identified epigenetic regulation of *CTGF* in our panel of pre-B ALL cell lines. Demethylation of CpG dinucleotides across the *CTGF* CpG island was a feature of *CTGF* positive cell lines, while those lacking *CTGF* expression were hypermethylated at this locus. The study has now been extended to included primary patient specimens. Future experiments aim to examine the effect of pharmacological modulation of CpG methylation upon *CTGF* expression in vitro.

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

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

CTL Cheung and UR Kees in collaboration with DH Strickland, Division of Cell Biology, and 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 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. *Ctgf* $^{-/-}$ mice die perinatally, owing to respiratory failure. Flow cytometry was used to enumerate the B, T and myeloid populations. *Ctgf* $^{-/-}$ neonatal livers were examined, and *Ctgf* $^{+/-}$ mice were studied and compared to wild type (WT) at 4 weeks and 8 weeks of age.

Initially we measured the content of B, T and myeloid populations in blood, bone marrow (BM), spleen, thymus and lymph nodes, comparing WT with *Ctgf* $^{+/-}$ mice. No significant differences were recorded. Interestingly, the neonatal liver cells of *Ctgf* $^{-/-}$ mice showed increased proportions of B cells and a decrease of myeloid cells compared to *Ctgf* $^{+/-}$ and WT liver cells. Taken together, we demonstrated that deletion of *Ctgf* influences the balance of B lymphopoiesis and myelopoiesis in mutant neonatal livers. To further examine the role of *CTGF* in HSCs and microenvironment, a series of transplantation experiments are under way; *Ctgf* $^{-/-}$ or *Ctgf* $^{+/-}$ HSCs are being transplanted into WT mice, to determine the repopulation capacity of cells.

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

OUTCOME PREDICTION OF PAEDIATRIC PATIENTS WITH ACUTE T-CELL LYMPHOBLASTIC LEUKAEMIA AT DIAGNOSIS

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

Continuous complete clinical remission in T-cell acute lymphoblastic leukaemia (T-ALL) is now approaching 80% due to the implementation of aggressive chemotherapy protocols, but patients that relapse continue to have a poor prognosis. Such patients could benefit from augmented therapy if their clinical outcome could be more accurately predicted at the time of diagnosis. Gene expression profiling offers the potential to identify additional prognostic markers, but has had limited success in generating robust signatures that predict outcome across multiple patient cohorts. This study aimed to identify robust gene classifiers that could be used for the accurate prediction of relapse in independent cohorts and across different experimental platforms. Using HG-U133Plus2 microarrays we modelled a five-gene classifier (5-GC) that accurately predicted clinical outcome in a cohort of 50 T-ALL patients. The 5-GC was further tested against three independent cohorts of T-ALL patients, using either qRT-PCR or microarray gene expression, and could predict patients with significantly adverse clinical outcome in each. The 5-GC featured the interleukin-7 receptor (*IL-7R*), low-expression of which was independently predictive of relapse in T-ALL patients. In T-ALL cell lines, low *IL-7R* expression was correlated with diminished growth response to IL-7 and enhanced glucocorticoid resistance. Analysis of biological pathways identified the NF-κB and WNT pathways, and the cell adhesion receptor family, particularly integrins, as being predictive

of relapse. Outcome modelling using genes from these pathways identified patients with significantly worse relapse-free survival in each T-ALL cohort. We have therefore used two different approaches to identify, for the first time, robust gene signatures that can successfully discriminate relapse and continuous complete remission patients at the time of diagnosis across multiple patient cohorts and platforms. Such genes and pathways represent markers for improved patient risk stratification and potential targets for novel T-ALL therapies.

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

MODELS OF DRUG-RESISTANCE TO PREDICT PATIENT OUTCOME IN ACUTE LYMPHOBLASTIC LEUKAEMIA

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

Children with acute lymphoblastic leukaemia (ALL) are treated with complex chemotherapy regimens of up to ten different drugs according to risk stratification at diagnosis. Around 80% of patients achieve continuous complete remission (CCR) with early response to drug therapy being one of the strongest predictors of outcome. However, a significant number of patients continue to relapse and for these the outlook is dismal due to the development of drug-resistance. Identifying potential markers of drug-resistance could improve patient stratification and further improve cure rates. Over the past 20 years our laboratory has developed a panel of paediatric ALL cell lines that retain critical features of the primary disease. Using the MTT viability assay we have measured the sensitivity of these cell lines to 13 commonly used ALL chemotherapeutic agents and have measured gene-expression profiles by Affymetrix HG-U133A microarray. In contrast to many of the cell lines that are available commercially, our cell lines generally grow at slow rates similar to the growth of leukaemic blasts *in vivo*. Their drug-resistance profile parallels the spectrum of resistance that has been observed in primary patient specimens, particularly in regard to dexamethasone. We have correlated drug-resistance and gene-expression profiles to generate an extensive database of drug-gene signatures that are currently being analysed for biological function. Comparison of drug-gene signatures with the publicly available Connectivity Map has provided potential drug-leads that are under test in our laboratory. We are also in the process of developing a gene expression-algorithm based on our *in vitro* drug-gene resistance data that can predict outcome in primary patient specimens. The data was used to generate a model of predicted resistance scores that was subsequently assessed in microarray datasets from three independent T-cell ALL (T-ALL) patient cohorts. These scores were used to predict patient outcome (relapse or CCR) in each cohort. The top 50 genes correlating with *in vitro* resistance to each of the ten drugs were used in modelling. Using this model, relapse/CCR patient status could be predicted with >75% accuracy in each of the three independent cohorts. Predictions of relapse were driven by contributions from different drug combinations in each of the cohorts, indicating particular importance in T-ALL therapy. These findings demonstrate that biological pathways correlating to *in vitro* drug resistance may have prognostic potential in patients and highlight the importance of understanding how individual patients relapse. These genetic features contribute to our understanding of drug resistance and represent potential markers for improved patient stratification at diagnosis.

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

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

AL Samuels, J Heng, AH Beesley and UR Kees in collaboration with KW Carter and RW Francis, Division of Biostatistics and Genetic Epidemiology.

Despite significant improvements in the treatment of childhood T-cell acute lymphoblastic leukaemia (T-ALL), up to 30% of patients will relapse and most of those face a dismal prognosis. Resistance to glucocorticoids (GC) is known to be a major factor contributing to the poor prognosis of relapsed ALL, however, it is still unclear how patients develop resistance and which pathways are deregulated. We predict that modulation of glucose metabolism pathways may be associated with drug resistance and evasion of apoptosis. To assess the bioenergetic phenotype we examined a panel of GC-resistant and sensitive T-ALL cell lines using *in vitro* cell culture assays to provide insights into the modulation of glucose metabolism and association with GC-sensitivity. These studies identified that glucocorticoid resistant leukaemia cells alter their central metabolism and enhance glucose catabolism. We found that GC-resistance is associated with an increased glycolytic phenotype and protection from metabolic crisis in T-ALL. Moreover, we have developed novel metabolomic and proteomic profiling techniques to identify metabolites and proteins associated with resistance, conducted in collaboration with Metabolomics Australia and Proteomics International. Preliminary metabolomic analysis also indicates that changes at the metabolic level are associated with drug resistance; we are currently identifying and delineating significant differentially expressed metabolites and pathways. Together these results indicate that drug-resistant leukaemia cells place unique importance on glucose as a carbon source and this relationship may provide a novel therapeutic opportunity. Understanding the metabolic/ proteomic mechanisms underlying the development of drug resistance in T-ALL is of critical importance for the identification of novel prognostic indicators and the development of more effective antileukaemic drugs.

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

TARGETING DRUG-RESISTANCE IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

AL Samuels, AH Beesley, V Peeva, and UR Kees in collaboration with R Papa 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 T-ALL non-obese diabetic/severe combined immunodeficient (NOD/SCID) xenograft model of leukaemia relapse. We have developed a novel, clinically relevant four-drug regimen to mimic in mice the initial phase of therapy in paediatric patients. Each xenograft was treated with vehicle control or a combination of vincristine, dexamethasone, L-asparaginase and daunorubicin (VXLD) to derive drug resistant clones *in vivo*. Importantly, the pattern of drug sensitivity in xenografts mirrored the progression of disease in the patients from whom they were derived.

We compared gene transcriptional profiles among the in vivo drug-selected T-ALL xenografts and controls to identify genes and pathways associated with drug resistance and ALL relapse (Samuels AL, Beesley AH, Lock RB, Kees UR et al. Validation of a Mouse Xenograft Model System for Gene Expression Analysis of Human ALL. *BMC Genomics*, 2010 Apr 21;11:256). Using this approach we were able to identify potential drug-leads that could synergise with current therapies to reverse the acquired drug resistance. Gene set enrichment and Ingenuity pathways analysis identified key networks, including cellular movement, carbohydrate metabolism and cellular death associated with drug resistance. The Connectivity Map algorithm predicted small molecule inhibitors to reverse the resistant phenotype, including those directed at histone deacetylase, beta-oxidative respiration and hydroxy-methyl-glutaryl Coenzyme A reductase (HMG-CoA). *In vitro* and *in vivo* screenings were conducted to assess the efficacy of several small molecule inhibitors targeting cellular metabolism pathways particularly fatty acid and lipid synthesis. One of the most promising drugs, an HMG-CoA inhibitor was evaluated *in vivo* as both a single agent and in combination with VXLD. Interestingly, we have found this modulator plus VXLD notably reduced leukaemic infiltration of the bone marrow 2 weeks post treatment initiation, this finding is currently being further evaluated. The results from our study indicated that patients develop distinct yet definable patterns of acquired drug resistance. Therefore to gain a thorough understanding of the mechanisms driving drug resistance and ALL relapse we are generating more xenografts. Primary engraftment for an additional 10 new T-ALL xenografts is underway. We will use transcriptional profiling to examine common and individual patterns among the xenografts to identify genes and pathways contributing to the resistant phenotype. 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 is supported by the NHMRC, Australia and the Children's Leukaemia and Cancer Research Foundation, WA.

CORRELATION OF NOTCH1 ACTIVATING MUTATIONS AND SENSITIVITY TO 6-MERCAPTOPURINE IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA CELL LINES

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

Acute lymphoblastic leukaemia (ALL) is the most common cancer in children, with T-cell ALL (T-ALL) occurring in about 15% of cases. Using the current Children's Oncology Group protocol 5-year event free survival rates approaching 80% can been achieved. However, for the patients that relapse many become resistant to the current chemotherapeutic drugs and a cure remains hard to achieve. *NOTCH1*, a critical developmental gene, was implicated in T-cell leukaemogenesis by the discovery of a t(7;9) translocation. More recently, activating mutations of *NOTCH1* have been demonstrated in over 50% of T-ALL patient specimens. Based on these observations we wished to (i) determine the mutational status of *NOTCH1* in our unique panel of T-ALL cell lines and (ii) to correlate the presence of *NOTCH1* activating mutations with the drug resistance profiles for these cells. DNA was extracted from 12 cell lines and *NOTCH1* exons were PCR amplified and sequenced. Activating mutations of the *NOTCH1* gene were identified in 7 of the panel of 12 cell lines (58%). One cell line had a mutation in the juxtamembrane domain, three cell lines had a mutation in the heterodimerization domain only, and one cell line had a mutation in the PEST domain, whilst two cell lines had mutations in both the heterodimerization and PEST domains. The drug resistance profile of the T-ALL cell line panel for standard chemotherapeutic agents used in the clinic to treat T-ALL (including cytosine arabinoside, 6-mercaptopurine, 6-thioguanine, methotrexate, dexamethasone, methylprednisolone, daunorubicin, doxorubicin, L-asparaginase and vincristine) were then correlated to *NOTCH1* mutation status. This revealed that cell lines with *NOTCH1* activating mutations were more susceptible to 6-mercaptopurine and 6-thioguanine than cell lines without *NOTCH1* activating mutations, indicating that they may be more important in T-ALL therapy than has been previously appreciated. We are currently expanding this research to include additional T-ALL cell lines and to study mutations in the *FBW7*, *PTEN*, *P53*, and *TPMT* genes, which have relevance either for *NOTCH1* signalling or thiopurine sensitivity. Such studies have important implications for improved risk stratification and the development of individualised treatment strategies.

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

INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA AND THE MIXED LINEAGE LEUKAEMIA (MLL) GENE

RS Kotecha, UR Kees, AH Beesley and NG Gottardo in collaboration with CH Cole and T Carter, Department of Haematology-Oncology, Princess Margaret Hospital and A Murch, King Edward Memorial Hospital for Women, Perth.

In modern medicine, treatment of paediatric acute lymphoblastic leukaemia (ALL) represents one of the many success stories, with significant improvements in event free and overall survival. However, infant ALL is a heterogeneous group with distinct biological and clinical characteristics, which continues to be resistant to this success. Infant ALL represents 2-5% of paediatric ALL cases. The most common genetic aberration in infant ALL involves the mixed lineage leukaemia (*MLL*) gene, located on chromosome 11q23, which is involved in up to 80% of cases. Most chromosomal rearrangements are associated with leukaemias of a particular lineage. However, 11q23 rearrangements are unique in that they occur in both ALL and acute myeloid leukaemia (AML), hence the term mixed lineage leukaemia. Since discovery of the *MLL* gene in 1992, its recombinome has been the subject of significant scientific research. There have been > 100 translocation partner genes identified, many of which have been characterized at the molecular level. *MLL-EPS15/AF1P*, t(1;11)(p32;q23) is a rare fusion, with a paucity of cases reported in the literature. We have recently reported infant monozygotic twins harbouring the t(1;11)(p32;q23) translocation which we are studying to obtain further evidence regarding the pathogenesis of this disease. Molecular analysis and sequencing has confirmed the breakpoint as a novel translocation breakpoint between the *MLL* and *EPS15* genes and we are continuing to analyse the features at the genomic level. DNA analysis using Affymetrix 2.7M Cytogenetic Arrays has provided evidence for additional copy-number variations affecting the leukaemias in both twins, challenging the concept that a single genetic defect is sufficient for overt disease in infant *MLL*. The identification of additional genetic abnormalities in such cases may provide opportunities for the development of novel targeted therapies in this disease.

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

Carcinomas

NOVEL BRD4 TRANSLOCATION IN UNDIFFERENTIATED CARCINOMA

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

Five years ago a 16-year old female patient was diagnosed at Princess Margaret Hospital (PMH) with a poorly differentiated lung carcinoma which had the hallmarks of a rare but almost invariably fatal carcinoma arising in the midline organs, known as a NUT midline carcinoma (NMC). These cancers are characterised by translocations between chromosome 15 and 19 and in most cases the breakpoint on chromosome 19 contains the *BRD4* bromodomain gene and the *NUT* gene on chromosome 15. This translocation was present in the cell line PER-403 established from an 11-year old girl diagnosed at PMH several years ago. The 16-year old patient received combination chemotherapy at PMH and she initially responded well, however died from disease 8 months after diagnosis. We generated cell line PER-624 from her cancer cells and have determined that they contain several karyotypic abnormalities, including t(6;19) and t(1;18;7) but not the standard translocation. FISH experiments were performed using whole chromosome paints, BACs, sub-telomere and PCR probes to determine the nature of these karyotypic abnormalities. These studies have shown that in this case *BRD4* and a region of 19p were cryptically inserted into chromosome 15, co-localising next to the *NUT* gene. To further characterise this carcinoma we used RNA sequencing to investigate the transcriptome. We identified that there is a *BRD4-NUT* fusion gene in the PER-624 cells but that it has a novel breakpoint which is different to the standard NMC cases. We have confirmed this breakpoint using RT-PCR. This novel fusion breakpoint, coupled with the FISH data suggests that there is alternative splicing occurring at the RNA level. We are currently undertaking genomic sequencing of the PER-403 and PER-624 cell lines to identify the exact nature of the genomic breakpoints in these cells. We also conducted a review of patient data from PMH and have identified another NMC case and two other carcinoma cases of interest. We have developed cell lines from these patient specimens and are conducting high-throughput drug screening in conjunction with the ACRF Drug Discovery Centre for Childhood Cancer, Children's Cancer Institute Australia, Sydney, to find alternative therapeutic strategies to treat this disease.

This work was supported by the Cancer Council Western Australia, Apache Energy, and the Children's Leukaemia and Cancer Research Foundation, WA.

THE NOVEL T-ALL AGENT FLAVOPIRIDOL: MECHANISMS OF ACTION AND RESISTANCE

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

Our recent studies in ALL cell lines have revealed that the novel agent flavopiridol (FP) is highly effective in steroid-resistant cells. When administered in a pharmacologically-derived schedule in adults and children, FP has been shown to achieve marked clinical efficacy in refractory haematopoietic malignancies, including acute leukaemias and relapsed high-risk chronic lymphoblastic leukaemia (CLL). Liposomes containing FP have recently been produced and this formulation has achieved significantly improved pharmacokinetics. However, the evidence that development of steroid resistance in ALL contributes to relapse makes it highly likely that clinical resistance to FP would also ultimately evolve, as has been the case for the drug Gleevec. The objectives of this study are to study the biological actions of FP and to derive FP-resistant ALL cell lines

with which to investigate potential mechanisms of FP-resistance before the phenomenon is known in the clinic. Over a period of two years we have grown cell lines in increasing concentrations of FP to generate clonal sublines with increased resistance to the drug. We now have 4 cell lines displaying approximately 2-fold higher resistance to FP than the parental lines. To establish the molecular basis for this change in phenotype, DNA extracted from these lines was analysed by Illumina TruSeq Exome Sequencing (AGRF, Brisbane). This data is currently being analysed and is expected to reveal the first genetic clues to the evolution of FP resistance. This knowledge will contribute to the application of this novel therapy to the treatment of drug-resistant ALL.

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

Paediatric Brain Tumours

THE IDENTIFICATION OF DEREGULATED GENES AND PATHWAYS INVOLVED IN THE PATHOGENESIS OF CHILDHOOD EMBRYONAL TUMOURS.

CM Bertram, LA Genovesi, UR Kees, JP McGlade, R Endersby, NG Gottardo, and PB Dallas.

Medulloblastoma (MB) is the most common type of malignant paediatric brain tumour. Although the five-year survival rate for standard risk MB patients is encouraging, the prognosis remains dismal for those with recurrent or metastatic disease. In addition, brain tumour survivors often face serious long-term quality of life issues that can profoundly affect patient and family. The relatively poor outlook for children with brain tumours can be largely explained by the fact that the molecular pathogenesis of MB is only partially understood. The main priority of the brain tumour research program is to address this problem, and ultimately develop safer and more effective drugs and treatment strategies that are urgently required. To achieve this goal we are employing a variety of approaches to investigate the molecular biology of MB.

A subset of MB is thought to arise from the deregulated proliferation of neural stem cells (NSCs) in the developing foetal brain. Hence, the development of MB is likely to be linked to the aberrant activity of signalling pathways that control NSC proliferation, self-renewal and differentiation. As part of our approach to identifying the genes that regulate these pathways, we have analysed chromosomal aberrations in a panel of paediatric brain tumour cell lines using cytogenetic analysis, representational difference analysis, and microsatellite mapping. To further refine our focus to specific regions of the human genome, we have correlated our extensive cytogenetic data with the gene expression profiles of our panel of brain tumour cell lines, primary tumour specimens, and human NSCs generated using Affymetrix HG-U133A microarrays. Cross-comparison of MB expression profiles with normal NSCs and differentiated neural tissues distinguished expression signatures associated with MB pathogenesis from signatures reflecting developmental variation. In addition, the study highlighted a genetic relationship between WNT and SHH-driven MB and CD133+ NSCs, as well as between MB with neuronal differentiation characteristics and foetal germinal matrix cells. Importantly, these data suggest that CD133+ NSCs represent a valuable *in vitro* model system for the study of the pathogenesis of SHH and WNT dependent MB and the development of more efficient subgroup-targeted treatment regimes in the future.

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

THE CHARACTERISATION OF DEREGULATED MICRORNA EXPRESSION IN PAEDIATRIC BRAIN TUMOURS

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

MicroRNAs (miRNAs) are a large class of short non-coding RNAs that regulate growth and development in eukaryotic cells. It is now clear that deregulated miRNA expression plays an important role in the pathogenesis of many different types of cancer, including adult brain tumours. Recent data suggest that deregulated miRNA expression may also play a significant role in the pathogenesis of MB. To address this issue in more detail we analysed the expression levels of a panel of 754 miRNAs in MB specimens and neural stem cells (NSCs) using qRT-PCR in a low-density array format. We identified 33 differentially regulated miRNAs in primary specimens relative to CD133+ NSCs. Interestingly, several of the over-expressed miRNAs were predicted to target *FOXO1A* raising the possibility that down-regulation of *FOXO1A* expression in MB may be linked to deregulated miRNA expression. We are currently investigating this possibility. Several deregulated miRNAs mapped to chromosome 14q32 and integrative analyses with inversely correlated predicted target genes revealed enrichment of pathways related to neuronal migration, nervous system development and cell proliferation. We anticipate that ongoing research based on these data will rationalise our understanding of the fundamental molecular mechanisms that initiate and maintain the brain tumour phenotype.

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

DEVELOPMENT OF A MOUSE EPENDYMOMA MODEL

H Hii, R Endersby, and NG Gottardo.

Ependymoma is the third most common brain tumour affecting children and remains incurable in 40% of patients. As is often the case with paediatric brain tumours, survivors are frequently left with devastating long-term neuro-cognitive sequelae. There is an urgent need for more effective and safer therapies. Transgenic mouse tumour models are important tools to facilitate the study of tumour initiation and progression and are invaluable for pre-clinical studies. A genome-wide analysis of human ependymoma specimens demonstrated that all cerebral ependymomas exhibited

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

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

TESTING NOVEL THERAPIES IN CHILDHOOD BRAIN TUMOUR MODELS

CL Burchill, PB Dallas, R Endersby, and NG Gottardo.

Medulloblastoma, pineoblastoma and ependymoma constitute the most common malignant brain tumours of childhood. Many children with these tumours remain incurable and survivors are often left with devastating long-term side effects. Whilst many novel targeted anti-cancer agents have been developed, to date only a small number have revealed clinical efficacy. One reason is due to the lack of model systems that accurately reflect the disease in children. To address this issue, we have previously generated a panel of unique cell lines, which have been cultured in the absence of drug selection, representative of the various medulloblastoma subtypes and pineoblastoma. In addition, to more closely model the tumours natural microenvironment, we have established an orthotopic xenograft mouse model system representative of the various medulloblastoma subtypes and pineoblastoma. We have also acquired a transgenic mouse model of medulloblastoma, the Smoothened (Smo) mouse, which develops spontaneous medulloblastoma due to the over-expression of the sonic-hedgehog pathway component Smo. We hypothesise that the use of these models will accelerate the investigation of combined conventional agents with targeted agents in clinical trials. Using the MTT cell proliferation assay we have determined the drug sensitivity profiles for our panel of brain tumour cell lines to conventional anti-cancer therapies currently used in the clinic for these tumours, including vincristine, cyclophosphamide, cisplatinum, lomustine (CCNU) and temozolomide. These profiles will form the basis for combinatorial studies using novel therapies. In addition, to uncover novel genes and biological pathways involved in the development of resistance to these drugs, we are also correlating the drug sensitivity profiles with the gene expression profiles.

We are currently assessing two novel compounds, alone and in combination with the chemotherapeutics above. The first compound, PF-00299804, developed by Pfizer, irreversibly targets the ERBB signalling pathway, which has been shown to be over-expressed in the majority of medulloblastomas and ependymomas. The second compound, CDDO-IM, a synthetic triterpenoid has shown anti-tumorigenic activity in many cancer types and been demonstrated to inhibit the anti-apoptotic protein *CFLAR/FLIP*. We found *CFLAR/FLIP* was significantly up-regulated in medulloblastoma samples relative to their putative normal cellular counterpart, implicating this gene in the development of medulloblastoma. We speculate that up-regulation of *CFLAR* in MB may be responsible for resistance to cytotoxic agents and that inhibition of *CFLAR* may sensitise cells to apoptosis. The best combinations, as determined from *in vitro* experiments, will then be assessed in our mouse model systems.

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

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

PB Dallas, J Varano, NG Gottardo, R Endersby in collaboration with N Milech, B Longville, R Hopkins, Drug Discovery Group, TICHR

Medulloblastoma (MB) is the most common malignant brain tumour in children, and a leading cause of paediatric cancer related mortality and morbidity. The disease is difficult to treat because there is a limited understanding of the molecular biology of these tumours. This has hampered the development of drugs that target the tumours specifically and minimise damage to normal tissues. Recently, drugs that target Smoothened (SMO), which is a component of the sonic hedgehog (SHH) pathway, have shown great promise for the treatment of MB. However, there are drawbacks with these new SMO targeting drugs, particularly associated with the development of resistance. Phylomers are a unique type of peptide-based drug developed by the drug discovery company Phylogica, which may be particularly suitable for avoiding the drug resistance problem. Phylomers have major advantages over other types of drugs, including the capacity to target large protein interfaces reducing the likelihood of the development of resistance, and the relative ease by which Phylomers can be engineered to access and enter tumour cells. In animal models, Phylomers have been shown to be effective for the treatment of burns, stroke and traumatic brain injury. The unique characteristics of Phylomers 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. Phylomers that target SMO, and other SHH pathway components, will be assessed for their ability to block tumour growth in cancer cell lines and animal models. Ultimately, this approach may radically improve the outlook for MB patients by providing new treatment options and opening up new avenues for drug development.

This research is supported by the Telethon Adventurers.

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RESEARCH SUPPORT

Stewart Cattach

Theses passed

Misty-Lee Palmer [Ph.D. 2011] "Paediatric acute lymphoblastic leukaemia cell lines to model clinical drug resistance and investigate MLL status". Curtin University of Technology, WA (Co-supervisor Dr U Kees and Prof M Garlepp)

Mathew Welch [Ph.D. 2011] "Molecular mechanisms underlying aberrant expression of connective tissue growth factor in paediatric pre-B cell acute lymphoblastic leukaemia." Curtin University of Technology, WA (Co-supervisors: Dr U Kees and Dr W. Greene)

Cornelia Bertram [Ph.D. 2011] "A human neural stem cell model for the study of medulloblastoma pathogenesis" University of Western Australia (Co-supervisors: Dr P Dallas and Dr U Kees).

Laura Genovesi. [Ph.D. 2011] "Characterisation of deregulated miRNA expression in paediatric brain tumours". University of Western Australia. (Co-supervisors: Dr P Dallas and Dr K Carter, and Dr K Giles, WAIMR)

Awards

Alex Beesley, Children's Leukaemia and Cancer Research Foundation (CLCRF) Travel Grant $4000.

Raelene Endersby. Professional Scientists Poster Award, Combined Biological Sciences Meeting, August 2011

External Committees

INTERNATIONAL

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

Nicholas Gottardo. Children's Oncology Group. Central Nervous System Tumour Committee

NATIONAL

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

Amy Samuels, Deputy convenor ASMR WA

Peter Dallas. Australasian Society for Stem Cell Research conference organising committee.

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

Nicholas Gottardo. Australian Children's Cancer Trials (ACCT) Principal Investigator.

Nicholas Gottardo. Australian Children's Clinical Trials (ACCT) group. Board member and Principal Investigator for Western Australia.

Raelene Endersby. Australian Early-Mid Career Researchers Forum, Australian Academy of Science.

Invited Presentations

Kees UR. 2011 OMICS Meet Cell Biology, Alpbach, Austria. May 2011 Profiling Drug Resistance in a Mouse Model of Leukaemia Relapse

Beesley AH (Invited Speaker 2011). High-throughput RNAi screening to dissect the molecular profile of NUT-Midline carcinoma. Perth Cancer Club, WAIMR.

Dallas PB. Cancer stem cells and brain tumours. Stem cells and their clinical applications: now

and the future. NSW stem cell network workshop. QEII Medical Centre. Perth, WA. Oct 2011.

Dallas PB. Novel peptide based drugs for the treatment of sonic hedgehog dependent medulloblastoma. Australian Children's Clinical Trials Symposium. Melbourne, Vic. June 2011.

Gottardo NG. Testing novel therapies using paediatric brain tumour models Australasian Biospecimen Network Association Annual Meeting. Perth, WA, Australia. Nov 2011.

Gottardo NG. The Children's Oncology Group: A blueprint for biobanking from clinical trials?. Clinical Oncological Society of Australia (COSA) ASM, Biobanking workshop. Perth. WA. Nov 2011.

Gottardo NG. Testing novel therapies using paediatric brain tumour models. Cooperative Trials Group for Neuro-oncology (COGNO) Annual Scientific Meeting. Sydney. NSW. Aug 2011.

Gottardo NG. Tumour Banking, a Clinicians Perspective. National Paediatric Tumour Banking Network Inaugural meeting. Melbourne. Vic. Feb 2011.

Gottardo NG. Testing novel therapies using paediatric brain tumour models. Australian Children's Cancer Trials (ACCT) Symposium. Australian Children's Clinical Trials Symposium. Melbourne, Vic. June 2011.

Endersby R. Developing novel mouse models for paediatric ependymoma. University of WA, Department of Pathology and Laboratory Medicine. Perth, WA, Nov 2011.

Endersby R. Use of a novel mouse glioma model for preclinical drug evaluation. Australian Children's Clinical Trials Symposium. Melbourne, Vic. June 2011.

Research Funding awarded (recent)

NHMRC Project Grant APP1011499 (2010): 'Targeting drug-resistance in childhood leukaemia' (Kees UR, Lock RB, Beesley AH, $626,732 over 3 years).

NHMRC Project Grant APP1007586 (2010): 'The role of connective tissue growth factor in the pathobiology of lymphoid tumours and response to therapy' (Kees, UR, Beesley AH, Charles AK, $601,732 over 3 years).

Children's Leukaemia and Cancer Research Foundation (CLCRF) Research Fellowship (2010): 'Targeting therapy and disease outcomes in paediatric cancer' (Beesley AH, 3 years).

NHMRC. NG Gottardo, R Endersby, U Kees. 2012-2014. Testing novel therapies using paediatric brain tumour models 2012-2014. $371,175.00

University of Western Australia Near Miss Safety Net Grant. NG Gottardo, 2011; $70,000

Cancer Council of Western Australia. PB Dallas, NG Gottardo, K Carter, K Giles. Project Grant 1006115. 2011-2012. The role of deregulated microRNA expression in the pathogenesis of medulloblastoma. $80000.

PMH Foundation Translational Research Grant. NG Gottardo and PB Dallas. Targeting apoptosis pathways in medulloblastoma. $48401

Pfizer Investigator initiated grant. NG Gottardo, PB Dallas, DM Ashley, TG Johns. A preclinical study of the effects of the pan-Her inhibitor PF-00299804 (PF) on the growth of brain tumour cells. $60400

ACTIVE collaborations

Children's Oncology Group, Arcadia CA, USA (Prof S Hunger and Dr S Winter collaboration with Alex Beesley and Ursula Kees)

St Jude Children's Research Hospital, Memphis TN, USA (Prof C Mullighan collaboration with Ursula Kees)

Walter and Eliza Hall Institute of Medical Research, Melbourne (Prof W Alexander and Dr R Dickins collaboration with Ursula Kees)

Children's Research Institute, Columbus OH, USA (Prof D Brigstock collaboration with Ursula Kees)

Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, UK (Dr M Garnett collaboration with Alex Beesley and Ursula Kees)

Experimental Therapeutics Program, Children's Cancer Institute Australia for Medical Research, Sydney (Prof M Haber and Prof M Norris collaboration with Alex Beesley and Ursula Kees)

Leukaemia Biology Program, Children's Cancer Institute Australia for Medical Research, Sydney (Prof R Lock; NHMRC Project Grants ID513765 and ID1011499 collaboration with Alex Beesley and Ursula Kees)

ACRF Drug Discovery Centre for Childhood Cancer, Children's Cancer Institute Australia for Medical Research, Sydney (Dr G. Arndt collaboration with Alex Beesley and Ursula Kees)

Department of Paediatric and Adolescent Haematology and Oncology, Princess Margaret Hospital for Children (Prof C. Cole, Dr M Phillips and Dr A Charles; NHMRC Project Grant ID 1007586 collaboration with Alex Beesley and Ursula Kees)

Lead Discovery Centre GmbH, Dortmund, Germany (NMC Carcinoma Project collaboration with Alex Beesley and Ursula Kees)

Novartis Pharma AG, Basel, Switzerland (NMC Carcinoma Project collaboration with Alex Beesley and Ursula Kees)

GlaxoSmithKline R&D, Brentford, UK (NMC Carcinoma Project collaboration with Alex Beesley and Ursula Kees)

Women and Brigham's Hospital, Boston (Dr Christopher French, Pathologist and International Expert in NUT-Midline Carcinoma collaboration with Alex Beesley and Ursula Kees)

Cytogenetics Department, King Edwards Memorial Hospital, Perth (Dr A Murch collaboration with Alex Beesley and Ursula

Kees)

Western Australian Institute of Medical Research, Perth (Prof Peter Leedman and Dr Keith Giles; miRNAs and cancer project collaboration with Peter Dallas, Raelene Endersby and Nicholas Gottardo)

Monash Institute for Medical Research, Melbourne. (Prof Terry Johns; New drugs for the treatment of paediatric brain tumours collaboration with Nicholas Gottardo, Raelene Endersby and Peter Dallas)

Pfizer Inc, New York, USA (New drugs for the treatment of paediatric brain tumours collaboration with Nicholas Gottardo, Raelene Endersby and Peter Dallas)

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 research into Type 1 diabetes, childhood onset Type 2 diabetes and obesity aims to improve 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 2011, type 1 diabetes research has seen the commencement of a series of clinical trials with the ultimate aim of implementing the closed-loop system of managing Type 1 diabetes using pump therapy. The year 2011 has also seen the culmination of a series of clinical trials in collaboration with AIMedics Pty Ltd, contributing to the development of a non-invasive monitoring system (HypoMon) for the detection of nocturnal hypoglycaemia. The Adolescent type 1 diabetes Cardio-renal Intervention Trial investigating the use of statin and ace-inhibitor to prevent diabetes complications is well underway, and recruitment to this study closes June 2012.

The group has also commenced a trial investigating the immediate and sustained benefits of incorporating a 12 week combined cardio and resistance training on microvascular and macrovascular health, of adolescents with Type 2 diabetes. The Bioenteric Intragastric Balloon study for weight management and health improvement in obese adolescents is now almost half-way though recruitment. Studies examining approaches to prevent hypoglycamia during exercise in patients with Type 1 Diabetes are also ongoing.

Type 1 Diabetes Epidemiology

EPIDEMIOLOGY OF CHILDHOOD-ONSET TYPE 1 DIABETES IN WESTERN AUSTRALIA

Liz Davis, Aveni Haynes, Matt Cooper, Carol Bower

Funding Source: Department of Endocrinology & Diabetes, PMH

The objectives of this study are:

To study the epidemiology of childhood onset diabetes in children aged 0-16 years in Western Australia from 1985 onwards.

To test for differences in incidence rates by year of diagnosis, age of diagnosis, sex, month of diagnosis, birth month and place of residence at diagnosis.

To identify potential antenatal and perinatal antecedents to childhood-onset diabetes e.g. birth weight, gestational age, birth order and maternal age.

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

EPIDEMIOLOGY OF HYPOGLYCAEMIA IN CHILDHOOD-ONSET DIABETES IN WESTERN AUSTRALIA

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 our which patients may be at higher risk of severe hypoglycemia.
The aims of this study are:

Report the incidence of severe hypoglycemia over the past decade in the WA childhood T1D onset cohort

Calculate the relative risk for the association of demographic, lifestyle and management factors (including but not limited too 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

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

Tim Jones, Liz Davis, Julie Dart, Heather Roby; Nirubasini Paramalingam; 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)

Tim Jones, Liz Davis, Niru Paramalingam

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.

IDENTIFYING MOLECULAR SIGNATURES OF TYPE 1 DIABETES

Prof Grant Morahan, Tim Jones, Liz Davis, Heather Roby

Funding Source: NHMRC 305500; Diabetes Research Foundation of WA

We aim to identify genes and genetic pathways associated with the autoimmune destruction of beta cells, and characterise the transcriptomic and proteomic changes of the T1D process. This will potentially

increase our understanding of the pathophysiology of T1D;

allow us to more finely stratify people most at risk of developing T1D;

discover biomarkers of the activity of the T1D process, which may allow clinical intervention in the "honeymoon period" before all beta cell mass is lost.

100 patients presenting to PMH with onset of T1D will be recruited to the study. Blood samples will be collected at diagnosis and at the 3-18 month follow-up clinic.

This study aims to measure changes in molecular systems at the time of onset of childhood T1D, and relate these changes to the patients' genotype for known T1D risk genes. The systems of interest are gene expression (transcriptome) in circulating WBCs and plasma protein composition (the plasma proteome) circulating WBC IFNγ production.

The approach of correlating gene expression and underlying genetic variation has recently been termed "systems genetics". The approach has been pioneered in rodent models, but has not been applied to proteomics, diabetes research or to research in humans.

The strength of this approach lies in the lack of assumptions that are taken into the data gathering process. Hypotheses are generated after data gathering and analysis. These hypotheses can then be validated using alternate "hypothesis-testing" experimental designs.

Type 1 Diabetes Management

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

Liz Davis; 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 ≤ 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

Tim Jones, Trang Ly, 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 6months can reduce the rate of severe hypoglycaemia, particularly for patients who have lost some of the symptoms that would normally alert them to a low blood glucose level. In a subgroup of 16 adolescents, we will also look at their hormone and symptom responses during hypoglycaemia.

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

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

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

Vinutha Shetty, Paul Fournier, Tim Jones, Liz Davis, Nirubasini Paramalingam, Adam Retterath, Heather Roby; 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 insulin treated type 1 diabetes individuals, particularly those in good glycaemic control, exercise increases the risk of severe hypoglycaemia.

This increased risk of hypoglycaemia occurs not only with 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 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 is affected by exercise intensity and how this relationship responds to confounding factors such as prevailing insulin and glucose levels. This study will involve one group 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 stationery bike at four different workloads – 35%, 50%, 65% and 80% VO2 Peak.

Primary outcome : Precise estimate of the glucose requirements to maintain stable glucose levels over a range of exercise intensities under basal insulin condition.

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

Type 1 Diabetes Technological Advances

PREDICTIVE LOW GLUCOSE SUSPEND STUDY – STAGE 1

Michael O'Grady; Trang Ly; Liz Davis; Tim Jones, Nirubasini Paramalingam; Julie Dart; Heather Roby; Adam Retterath

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 analyse the pattern of blood glucose and ketone levels following pump suspension in both scenarios, and use these to assist with determination of parameters for insulin pump resumption.

Type 1 Diabetes Complications

ADOLESCENT TYPE 1 DIABETES CARDIO-RENAL INTERVENTION TRIAL

Tim Jones; Liz Davis, Barbara Sheil; Julie Kendall; Heather Roby; Trang Ly; Vinutha Shetty; Michael O'Grady; Adam Retterath; Jennifer Nicholas

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 closes in June 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

Tim Jones; Liz Davis, Julie Kendall; Julie Dart; 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. The study duration

Is 6 years, and includes a two year recruitment period and a 4year follow-up period. The study endpoints are changes in retinal images, aIMT and heart rate variability measures, after 4 years duration from baseline.

NEUROCOGNITIVE OUTCOMES OF CHILDREN WITH TYPE 1 DIABETES MELLITUS

Tim Jones; Mike Anderson; Liz Davis, Kaitie McNamara; Nooshi

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

Type 1 Diabetes Prevention

INTRANASAL INSULIN TRIAL II

Liz Davis; Tim Jones, Julie Kendall; Trang Ly; Vinutha Shetty; Michael O'Grady; Nirubasini Paramalingam; 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

Tim Jones; Liz Davis, Julie Dart; Heather Roby; Nirubasini Paramalingam; 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 Epidemiology

EPIDEMIOLOGY OF T2DM IN CHILDHOOD AND ASSOCIATED DISEASE COMPLICATIONS

Liz Davis; Rachelle kalic

Funding Source: Internal

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

Type 2 Diabetes Management

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

Liz Davis; Danny Green; Louise Naylor, 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

Liz Davis

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

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

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

Intervention

BIOENTERIC INTRAGASTRIC BALLOON

Jacqueline Curran; Liz Davis; Colin Sherrington; Tim Jones, 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 recruited to the study.

Repositories and Databases

TYPE 1 AND TYPE 2 DIABETES DNA BANK

Tim Jones; Liz Davis

Funding Source: Department of Endocrinology & Diabetes, PMH

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

Grant Morahan; Tim Jones; Liz Davis, 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

Tim Jones; Liz Davis, 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

Tim Jones; Liz Davis

Funding Source: Internal Funds

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

Liz Davis, Rachelle Kalic

Funding Source: Internal

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

Liz Davis; Tim Jones; Sue Byrne; Jacqueline Curran, Rachelle 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 Note Dame Australia

SENIOR TEAM LEADER

Liz Davis MBBS , FRACP, PhD
Clinical Associate Professor, University of Western Australia
Head, Diabetes and Obesity Services, Princess Margaret Hospital for Children
Associate Professor, School of Paediatrics and Child Health, The University of Western Australia
Faculty Member - Senior Principal Investigator, Telethon Institute for Child Health Research, The University of Western Australia

RESEARCH STAFF

Raymond Davey PhD

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

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Jennifer Nicholas BSc (Nursing), CDE, MSc (Diabetes Education)

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

Adam Retterath BSc(Hons)

Heather Roby BSc

Barbara Sheil PhD

POSTGRADUATE STUDENTS

Matthew Cooper BSc, PhD candidate

Aveni Haynes BA(Hons), MBBChir, PhD candidate

RESEARCH SUPPORT

Mary Flynn Grad Dip(Counseling), BA (Fine Art)

Theses passed

Liz Davis, PhD, University of Western Australia: Glucokinase – From kinetic analysis to clinical application and a novel therapeutic potential

Awards

Tim Jones, Diabetes Australia Research Trust Award 2005

Tim Jones, Mary Jane Kugel Award: Medical and Scientific Review Committee, Juvenile Diabetes Research Foundation 2004

Tim Jones, APEG: Norman Wettenhall Medal for Excellence in Research & Innovation – Paediatric Endocrinology 2011.

Liz Davis, Prize for Clinical Medicine, University of Western Australia, 1985

Liz Davis, Award for best scientific paper at West Australian College of Paediatrics Research Seminar. 1993.

Ray Davey, Young Investigator Award, ADS-ADEA meeting. 2011

External Committees

INTERNATIONAL

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

Tim Jones. JDRF Artificial Pancreas Consortium – Member 2011

Tim Jones. Medtronic Advisory Board Clinicians – Member 2011

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

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

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

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

Tim Jones. JDRF Professional Advisory Panel- 2007

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

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

Liz Davis. Australasian Paediatric Endocrine Group - 2011-Member of Executive Council 2011 - 2012

Liz Davis. Australasian Paediatric Endocrine Group - 2005- Member Diabetes Database Committee – 2005 - 2012

NATIONAL

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. Type 1 Diabetes Guidelines Expert Advisory Group – Member

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

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

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

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

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

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

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

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

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

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

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

Liz Davis. Diabetes Research Foundation – board member 2004

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

LOCAL

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

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

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

New Children's Hospital WA Advisory Group – Member 2011

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

Invited Presentations

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

Tim Jones. International Diabetes Federation Congress, Mexico 2000.

Tim Jones. NZSSD Annual Scientific Meeting, May 2001.

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

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

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

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

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

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

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

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

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

Tim Jones. Intensive Insulin Therapy. Lawson Wilkins Paediatric Endocrine Society/European

Society for Pediatric Endocrinology, New York NY USA, September 2009.

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

Tim Jones. Diabetes in Children (Plenary); Technology in Type 1 Diabetes Therapy; Pediatric Care (Discussions) Diabetes Asia 2010, Kuching, Malaysia Oct 2010.
Tim Jones. Insights into the Future of Glucose Management - Managing Hypoglycemia: a prospective view of GCM technologies. at 5th International Conference, Advanced Technologies & Treatments for Diabetes, Spain. Feb 2012

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

International Society of Paediatric and Adolescent Diabetes Conference, Durban 2008

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

Australasian Paediatric Endocrine Group Annual Meeting, Canberra 2008

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

Liz Davis. T2DM in WA – Annual meeting of WA Diabetes Educator Association. Invited speaker, May 2009

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

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

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

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

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

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

ACTIVE collaborations

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

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

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

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

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

Prof Grant Morahan: Western Australian Institute for Medical Research

Mr Victor Skladnev: AIMedics Pty Ltd, NSW

Prof Hung Nguyen: University Technology, Sydney, NSW

Winthrop Prof Mike Anderson: School of Psychology, UWA

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

DRUG DISCOVERY

Overview

The Drug Discovery Technology Unit (DDU) and its commercialization vehicle Phylogica Ltd.

The Drug Discovery Technology Unit is focused on developing therapeutic approaches against disease-associated protein interaction targets both inside and outside of cells as well as the development of 'mimetic' vaccines against discontinuous epitopes. The research of the unit is funded by contracts with large pharmaceutical companies via a commercial entity named 'Phylogica' which was the first spin-off company from the Telethon Institute for Child Health Research.

Phylogica (http://www.phylogica.com) which is listed on the Australian Stock Exchange, is a specialist drug discovery company, which indentifies new prototype drugs for large drug company customers (www.phylogica.com). It achieves this by drawing from its own huge source of billions of unique compounds from nature, the world's largest and most diverse collection (see below). These are strongly protected by a portfolio of 16 patent families, including granted patents in the US and Europe. The peptide drug class which Phylogica controls access to is known as "Phylomers'.

Phylomers: The world's most structurally diverse library of peptides

Phylogica's proprietary Phylomer® libraries contain billions of distinct peptides that represent a rich source of biologically active drug leads for a broad range of intracellular and extracellular disease targets. The Phylomer® libraries are based on expressed sequences of protein fragments that are encoded by the natural genes of evolutionary diverse microbes that often exist in extreme environments such as deep sea volcanic vents and geysers. Typically, these peptides, which are known as Phylomer® peptides, are comprised of 15 to 50 amino acids. The inherent diversity of the genetic sources of Phylomer® peptides means that libraries contain multiple classes of subdomain and supersecondary structures across thousands of distinct structural families. Phylomer® peptides can show excellent specificity can function as high affinity disruptors of protein-protein interactions and binders of protein targets. Since Phylomer® libraries have the most comprehensive collection of distinct protein-based structures available this gives them a key versatility advantage over other peptide libraries This feature of high structural diversity has resulted in Phylomer® libraries successfully yielding high quality functional primary hits (pM- nM affinity), against multiple classes of intracellular and extracellular drug targets as well as in direct phenotypic screens. Phylomer® libraries have a number of advantages against a range of alternate random peptide screening technologies for biologic discovery. This leads to their diverse application in a range of distinct areas (see figure 1 below).

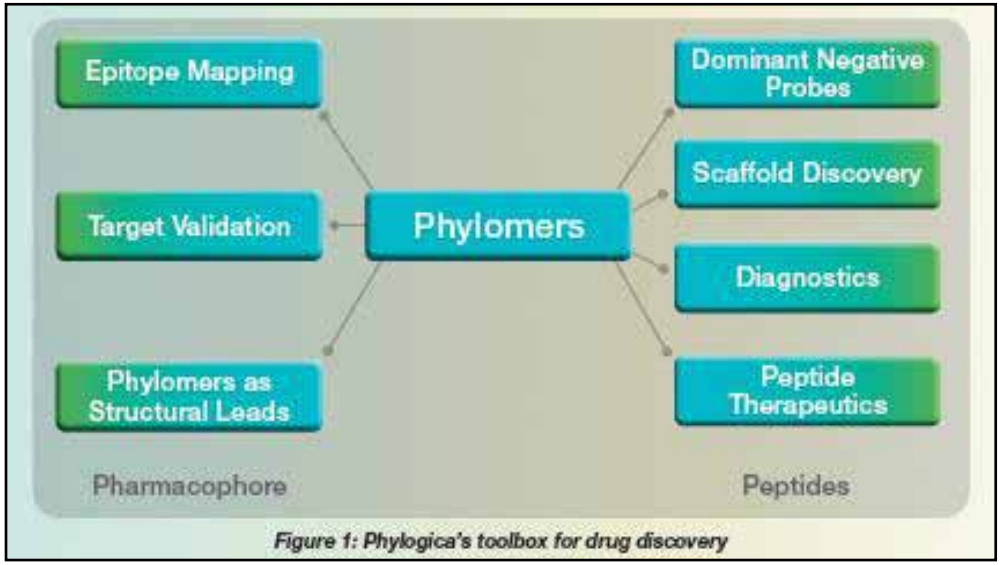


Figure 1: Phylogica's toolbox for drug discovery

Extracellular Targets (GPCR's and other receptor)

BLOCKING THE INFLAMMATION TARGET CD40 LIGAND (CD40L)

Katrin Hoffmann, Shane Stone, Paula Cunningham and Richard Hopkins

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

DISCOVERING NEW ANTIMICROBIALS AGAINST MULTI-RESISTANT MICROORGANISMS

Tatjana Heinrich and Richard Hopkins

The Drug Discovery Technology Unit has had extensive experience in the discovery of antimicrobial peptides from its phylomer libraries. Some of these peptides have activity on multiresistant isolates of *Acinetobacter baumanii*, an important cause of hospital acquired infections of burns patients. We have also screened Phylomer libraries to identify and characterize antimicrobial peptides

against the related pathogen *Pseudomonas aeruginosa*, which is involved in hospital-acquired catheter and burns infections as well as lung infection, particularly in children suffering from cystic fibrosis. The group has investigated the biophysical properties of antimicrobial Phylomer peptides by a technique known as circular dichroism. These studies measure the extent of formation of the alpha helix structure in model membranes incorporating various phospholipid mixtures which mimicking different types of bacteria or mammalian cells. These studies found good agreement between prediction *in silico* and biophysical measurements. We also were able to optimize antimicrobial Phylomer peptides - reduced length to approximately 20 amino acids and improving the activity (MIC) to the high nanomolar range. Recent studies have explored the potential synergy between clinical antibiotics and antimicrobial Phylomer peptides and found at least one potent combination. We have found a number of peptides with antimicrobial activity against the nosocomial infective agent *Pseudomonas. aeruginosa*. We have established a control panel of recently published, highly active natural antimicrobial peptides and compared them with antimicrobial Phylomer peptides under different salt conditions (different broths), and have identified Phylomer derivatives which are more active than a potent antimicrobial peptide known as Tachyplesin which is isolated from the horse-shoe crab.

Intracellular Targets and Novel Delivery Approaches

DISCOVERY AND CHARACTERISATION OF NOVEL CELL PENETRATING PHYLOMERS

Katrin Hoffmann and Richard Hopkins

The emerging field of cell penetrating peptides (CPPs) is generating considerable excitement in the pharmaceutical industry. Not only can this class of peptide be used to deliver existing drugs inside cells but they also provide access to an entirely new landscape of intracellular targets. Indeed, estimates suggest that 80% of 'druggable' targets are located inside cells. Combined with the fact that CPPs can deliver new classes of drugs such as biologics into cells, one can appreciate why CPPs have the potential to significantly expand the landscape of targets currently considered druggable.

Phylogica has screened its Phylomer® libraries to identify peptides that can deliver drugs into cells. These efforts yielded approximately 1000 unique candidates, highlighting the structural and functional diversity present within our Phylomer® libraries. After screening a sub-pool of 166 Phylomers, a total of 17 peptides were confirmed as having cell penetrating activity, corresponding to a functional hit rate of 11%.

Most importantly, our recent analysis has identified multiple classes of novel cell penetrating Phylomers (Table 1). These peptides range from the traditional short, positively charged CPPs, to Phylomer® peptides that mimic invasive viral peptides involved in cell entry and escape into the cytoplasm.

For example, the sequence of one of our novel cell penetrating Phylomers is analogous to a viral peptide found in the Simian Immunodeficiency Virus. We have also identified cell specific Phylomer® peptides and others that are aligned to bacterial virulence factors known to be involved in cell invasion (for example: the fibronectin binding protein from *Staphylococcus aureus*).

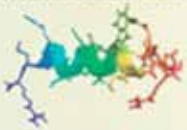
Class	Phylomer®	Comments
1	BEN_1079	• Conventional cationic amphipathic cell penetrating peptide 
2	BEN_0805	• Similar to gp41 protein transmembrane protein from Simian Immunodeficiency Virus • Facilitates fusion between viral and cell membranes
3	BEN_5000	• Derived from a natural transposase protein • Exhibits cell selective uptake in brain endothelial cells • Focus of additional studies with Roche
4	BEN_1312	• Derived from fibronectin binding protein from S. aureus • Virulence factor known to play a role in cell invasion

Table 1: Multiple classes of validated cell penetrating Phylomers

Our ability to enrich for different classes of peptides with natural cell penetrating activity is unique to our Phylomer® technology and has generated considerable interest with prospective Pharma partners.

Phylogica is currently developing a second generation screening platform, which promises to improve significantly on the diversity and quality of cell penetrating Phylomers that can be isolated.

Intracellular Projects and Target Discovery

ANTICANCER PHYLOMERS: TARGETING 'SONIC HEDGHOG'

Nadia Milech and Richard Hopkins in collaboration with Peter Dallas and Nick Gottardo, Division of Children's Leukaemia and Cancer Research

The 'Sonic hedgehog' pathway earned its name after researchers observed that cells of fruit flies, which carry a mutation in the gene encoding hedgehog ligand, have a spiky appearance. The mammalian equivalent of this gene was named 'Sonic hedgehog' (Shh) as a humorous reference to a video game of the same name. Inappropriate inactivation of this

pathway causes cancer and is associated with malignancies such as basal cell carcinoma, which is a form of skin cancer, and a childhood brain cancer known as medulloblastoma (Figure 2).

Screens of our Phylomers against two independent targets in the Shh pathway have yielded over 100 potentially interesting peptides. Having screened approximately half of these hits for functional activity in two industry-standard in vitro assays, we have identified some very promising lead candidates for further development.

These Phylomer® leads will be further evaluated to determine their suitability for assessment in a predictive preclinical in vivo model of medulloblastoma that has been established by our collaborators within the Telethon Institute of Child Health Research.

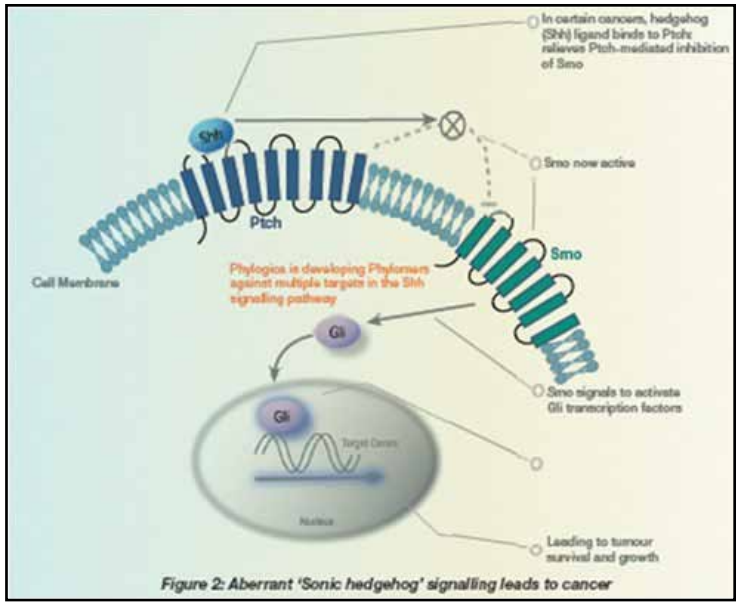


Figure 2: Aberrant 'Sonic hedgehog' signalling leads to cancer

PHENOTYPIC SCREENING FOR TARGET DISCOVERY & VALIDATION

Paul Watt, Nadia Milech and Richard Hopkins, in Collaboration with Cambridge University

The Drug Discovery Technology Unit has been collaborating with Ashok Venkitaraman, the distinguished Professor of Oncology of the Hutchison MRC Unit at the University of Cambridge in the UK.

The objective of this collaboration has been to test if Phylomer libraries might assist in identifying new cancer targets for the discovery of new drugs. The Hutchison group has shown the Phylomers can bind to defined targets linked to cancer cells, and that the hit-rate in a phenotypic mammalian screen of a Phylomer library is superior to that from traditional approaches used by pharmaceutical companies.

Having achieved this aim, the next relevant step was to use the target binding as a tag to identify the key biological step in a pathway for which new drugs might be built. The success of the target identification using the Phylomers in this collaboration highlights the usefulness of this approach for target discovery.

It has subsequently been shown that a phylomer can be used both to identify a candidate target as well as to validate that target via 'protein interference'. It is expected that this target validation at the protein level, will be very useful as it provides an opportunity to block disease-relevant interfaces of target proteins while not blocking their normal functions.

To commercially exploit this opportunity, a new commercial entity named 'Phenomica' has been created as a joint spin-off between Phylogica and the University of Cambridge. There is already interest from the Pharmaceutical industry in accessing the expertise of Phenomica in phenotypic screening for target discovery and validation.

Staff and Students

PRINCIPAL PROGRAM MANAGER

Paul Watt BSc.(Hons) D.Phil (Oxon)
Member of Faculty, Drug Discovery Division
Adjunct Professor, University of Western Australia

RESEARCH STAFF

PROGRAM MANAGER

Richard Hopkins, BSc. (Hons) PhD
Member of Faculty, Drug Discovery Division

TEAM LEADERS

Katrin Hoffmann BSc (Hons), PhD Cell Penetrating Peptide Discovery/Phage

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

Shane Stone BSc (Hons), PhD Structural Biology/ Modeling &Bioinformatics

Paula Cunningham BSc (Hons), PhD Inflammation and Bioassay Development

Tatjana Heinrich BSc (Hons), PhD Antimicrobial Discovery

RESEARCH STAFF

Mark Anastasas BSc (Hons)

Allan Beveridge BSc, MSc, PhD

Tracy Chai BSc (Hons)

Clinton Hall BSc (Hons)

Suzy Juraja BSc (Hons), MSc, PhD

Maria Kerfoot BSc (Hons)

Brooke Longville BSc (Hons), PhD

Marie Scobie BSc (Hons)

Sarah See BSc (Hons), PhD

Yew-Foon Tan BSc (Hons), PhD

Susan Turner BSc (Hons)

Scott Winslow BSc (Hons)

SUPPORT STAFF

Farzana Khan BSc (Hons)

Leanne Neville

Awards

Paul Watt, 2011 WA Finalist for the Ernst and Young Entrepreneur of the Year Awards and one of 3 finalists nationally for the Rio Tinto Commercialisation of Innovation Eureka Award of the Australian Museum.

Paul Watt, 2011 Winner of Asia Pacific Frost and Sullivan New Product Innovation Award for Phylomer Technology

External Committees

Paul Watt, University of Western Australia, 'Pathfinder' commercialization

Richard Hopkins, Ausbiotech, Western Australian Committee

Invited Presentations

Paul Watt Feb 22-24th 2011, Biocom Global Life Science Partnering Meeting, La Jolla

California USA

Paul Watt April 12-14, 2011, BioTrinity 2011 Meeting, Newbury

Paul Watt May 23-25, 2011, IBC TIDES Conference, Boston

Paul Watt June 8-9th, 2011, Oxford Global R&D Leaders Summit, Zurich

Paul Watt June 20-22, IBC Protein Therapeutics Summit, San Francisco

Paul Watt September 7th-9th, Biopharm America Boston

Paul Watt December 5-7th , Natural Peptides To Drugs (N2PD) Zermatt,Switzerland

Richard Hopkins Feb, 2011: Roche Peptide Symposium, Colorado

Richard Hopkins June 2011: IBC Next Generation Protein Engineering Summit, San Francisco

Stone, S.R., Hoffman, K., See, S., Milech, N., Anastasas, M., Hall, C., Hellsten, R.L., Thompson, C.A., Juraja, S., Cunningham, P.T., Scobie, M.N., Winslow, S.G., Watt, P.M., and Hopkins, R.M., (2011), Anti-CD40L Phylomers®: De Novo Modelling of Phylomer®-CD40L Interactions, 9th Australian Peptide Conference: Peptides – by Discovery and Design, Hamilton Island QLD, October 2011.

Stone SR, Hoffmann K, Milech N, Anastasas M, Hall C, Hellsten RL, Thompson CA, Juraja S, Cunningham PT, Scobie MN, Winslow SG, Watt PM, Hopkins RM., (2011), Anti-CD40L Phylomers®: De Novo Modelling of Phylomer®-CD40L Interactions, Drug Discovery Chemistry: Peptide-Peptide Interactions, San Diego CA, April 2011.

Collaborations

Dr Erica Golemis, Fox Chase Cancer Centre (Philadelphia) - (Blocking protein interactions, Yeast Two Hybrid Screening

Dr Reto Crameri Swiss Institute of Allergy and Asthma Research (SIAF, Davos), Mimetopes of allergens

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

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

Professor Una Ryan, Murdoch University, WA. Cryptospiridium

Associate Professor Marie Bogoyevitch, University of Melbourne (Bio21 Institute), VIC

Professor Adrian West, University of Tasmania, TAS

Adjunct Associate Professor Bruno Meloni and Professor Neville Knuckey, Australian Neuromuscular Research Institute, WA

INFLAMMATION

Overview

Sunlight is one of the most important environmental agents to which man is exposed. The ultraviolet B (UVB) wavelengths are the most powerful and cause not only skin cancers, but also suppression of immune responses to antigens introduced at distant body sites. We have previously shown that UVB light administered to the shaved dorsal skin of mice can suppress models of allergic airways disease. This suggested that UV-induced changes in the skin could signal downstream systemic responses to allergens in respiratory tissues. In 2011, we focussed on the effects of UV irradiation of skin on dendritic cell precursors in the bone marrow. This was important as the bone marrow produces haematopoietic cells that replace those that are dying in the peripheral organs. Erythemal UVB irradiation of skin stimulated the production from bone marrow of poorly functioning dendritic cells. Further, UV-induced prostanoids were responsible for the effects of UV irradiation of skin on dendritic 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. The 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 investigated whether inflammation in other tissues had the same effect on dendritic cell precursors in the bone marrow. In further studies, we have shown that inflammation of the respiratory system and in the peritoneal cavity induces the formation of less immunogenic, regulatory dendritic cells from bone marrow by a prostanoid-dependent process.

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

In 2011, our studies of the mechanism of action of interleukin-4 as an anti-inflammatory cytokine for human monocytes and macrophages continued. Gene arrays gave new candidate molecules that may be involved in the mechanism by which IL-4 suppresses inflammatory mediator production. These studies are ongoing.

Inflammation

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

NM Scott, J Bisley, RLX Ng, PH Hart

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

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

EFFECT OF UVB ON BONE MARROW CELLS ENGRAFTED INTO CHIMERIC MICE

RLX Ng, NM Scott, SA Bazely, DH Strickland, S Gorman, PH Hart.

Regulatory dendritic cells are generated by culture of bone marrow from UV-irradiated mice and results suggest the induction of regulatory cells. We are uncertain of the potential artificial effect of bone marrow cell culture. In 2011, chimeric mice were established; mice were gamma-irradiated to destroy their bone marrow cells and then injected with bone marrow cells from non-irradiated or UV-irradiated mice. The re-establishment of their bone marrow was followed and by 8 weeks, the peripheral lymph nodes had been re-populated. After 16 weeks, the efficiency of the engrafted dendritic cells has been sought as we wish to know whether the effects of the UV exposure are long-lived. When an inflammatory antigen is painted on the skin of the chimeric mice, there is an inflammatory response in mice engrafted with bone marrow cells from non-irradiated mice but a very poor response if the mice were engrafted with bone marrow cells from UV-irradiated mice. This result suggests a long lasting effect of UV irradiation on dendritic cells in the bone marrow.

Funded by NHMRC, UWA Postgraduate Award to RN & SB, Perron award to RN & SB.

EFFECT OF UVB ON BONE MARROW SUBPOPULATIONS

SA Bazely, R Ng, N Scott, DH Strickland, S Gorman, PH Hart.

The effect of mature dendritic cells in the bone marrow on the development of regulatory dendritic cells in culture has been investigated by their removal prior to culture of the bone marrow cells. No consistent effect was measured. As poorly immunogenic dendritic cells are generated under all differentiative conditions (namely upon culture with GM-CSF or FLT-3L), we speculate that an early dendritic cell progenitor is altered by UV irradiation of skin. We have FACS-sorted early dendritic cell progenitors (Lineage negative, CD117 positive) from bone marrow of mice obtained 3 days after UV-irradiation of the shaved dorsal skin of the mice. RNA was extracted from the cell populations and we have recently sent RNA preparations externally for microarray analysis. We propose that differences in the transcriptomes of the dendritic cell progenitors from the bone marrow of non-irradiated and UV-irradiated mice will help us understand how the developmental programme of the dendritic cells is altered by UV-irradiation of skin.

Funded by NHMRC, UWA Postgraduate Award to SB & RN, Perron award to SB & RN.

EFFECT OF EXPERIMENTAL ALLERGIC AIRWAYS DISEASE AND THE INFLAMMASOME ACTIVATOR, ALUM, ON BONE MARROW-DERIVED DENDRITIC CELLS

NM Scott, J Bisley, RLX Ng, PH Hart.

In response to UV-induced inflammation of the skin, bone marrow derived dendritic cells are regulatory. To determine whether the effect is unique to skin inflammation, the effect of inflammation at other tissue sites has been examined. In response to inflammation in the airways and in the peritoneal cavity (due to administration of the inflammasome activator, alum), bone marrow derived dendritic cells are regulatory. Further their development is blocked by the administration of indomethacin and again suggests that inflammation-induced PGE_2, and possibly prostanoids, are responsible. 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 tissue inflammation.

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

VITAMIN D IN DEFICIENCY – EFFECT OF DIETS DEFICIENT IN VITAMIN D3

S Gorman, C Weedon, PH Hart

To study vitamin D_3 deficiency, we have established colonies of BALB/c mice fed a vitamin D restricted diet. The ovalbumin-driven model of allergic airways disease has been established in these mice. Detailed studies suggest that the models of disease are worse in the vitamin D-deficient mice supporting the hypothesis that vitamin D has a regulatory role in systemic immune diseases such as asthma. Effects of vitamin D deficiency have been measured in both the lymph nodes and the lungs and airways. The effects of vitamin D were more important when lower concentrations of allergen were used to develop the model. Studies are in progress to examine the effect of vitamin D deficiency on the various immune cell types, particularly dendritic cells.

Funded by the Brightspark Foundation and the Raine Foundation

VITAMIN D IN DEFICIENCY – EFFECT OF UV IRRADIATION OF SKIN

S Gorman, C Weedon, NM Scott, PH Hart

When vitamin D_3-deficient mice are UVB irradiated, only the female mice are able to respond with systemic vitamin D_3 levels. We do not fully understand why male vitamin D_3-deficient mice are unable to make circulating vitamin D_3 although they are able to make vitamin D_3 if it is provided in their diet. We believe that we have developed a powerful model to determine which immunoregulatory responses measured following UVB irradiation of skin are vitamin D_3-dependent. In assays of both systemic and local contact hypersensitivity, and OVA-induced asthma, male and female mice have responded to UV irradiation to a similar extent. We have not detected responses to UV in male vitamin D_3-deficient mice that are vitamin D_3-dependent. To better understand why the skin of male mice cannot respond to UV irradiation, the expression of the enzymes responsible for the development and breakdown of vitamin D are being investigated.

MECHANISMS OF REGULATION BY IL-4 FOR REDUCED INFLAMMATORY MEDIATOR PRODUCTION BY HUMAN MONOCYTES

EA Woodward, PH Hart.

We have been studying the mechanisms by which interleukin-4 (IL-4) can suppress inflammatory cytokine production by activated human monocytes and macrophages. Using gene arrays, we continue to search for molecules that may be involved in the anti-inflammatory properties of IL-4. Candidate molecules studied in 2010 include RP-105 (CD180), IL-10, RIPK2 and the transcription factor c-Maf.

Funded by Murdoch University Students stipend, Perron award to EAW

Staff and Students

RESEARCH STAFF

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

Shelley Gorman BSc (Hons) PhD

Naomi M Scott BSc (Hons)

Jacqueline Bisley BSc (Hons)

Clare Weedon BSc (Hons)

POSTGRADUATE STUDENTS

Eleanor A Woodward BSc (Hons), PhD Candidate

Royce LX Ng BSc (Hons), PhD Candidate

Scott A Bazely BSc, PhD Candidate

Awards

Prue Hart, Adjunct Professor, University of WA, NHMRC Principal Research Fellowship

Shelley Gorman, Brightspark Research Fellowship 2011-1013.

Royce Ng, Best Student Presentation, Australasian Society for Immunology, Annual State Meeting, October 2011

Presentations

PH Hart, Poster Presentation, Keystone Symposium, 'Immunoregulatory Networks', Beaver Run Resort, Breckenridge, USA, April 2011.

PH Hart, Public Lecture, Telethon Institute for Child Health Research, July 2011. Vitamin D: Super nutrient or super fad?

PH Hart, Invited Seminar speaker, WAIMR, August 2011

PH Hart, Invited speaker, European Society for Photobiology 14th Congress, Geneva, Switzerland, September 2011.

PH Hart, Invited speaker, Australian Thoracic Society, WA Conference, Mandurah, October 2011.

PH Hart, Symposium on 'Giving Advice on How Much Sun Exposure Should We Get', organised by the Cancer Council WA, Perth, November 2011.

PH Hart, Invited symposium speaker, Japanese Society for Investigative Dermatology - Asia-Oceania Symposium, Kyoto, Japan, December 2011.

S Gorman, Research Presentation, secondary-aged school students from Ashdale Secondary College and year 12 students attending the National Youth Science Forum visiting TICHR, January 2011.

S Gorman, Invited presentation, Australian Society for Dermatology Research National Conference Perth, May 2011.

S Gorman, Public Lecture, Telethon Institute for Child Health Research, July 2011. Vitamin D: Super nutrient or super fad?

S Gorman, Research Presentation, primary-aged school students at St Hilda's Anglican School as part of National Science Week (Being a Scientist, September 2011).

S Gorman, Seminar, Perspectives in Child Health Research Seminar, TICHR, August 2011

S Gorman, Perth Immunology Group Meeting, Australasian Society for Immunology, Perth, October 2011.

S Gorman, Australasian Society for Immunology Annual Scientific Meeting, Adelaide, December 2011.

Royce Ng, The Australasian Society for Dermatology Research (ASDR), Annual National Meeting, Perth – May 2011

Royce Ng, Australian Society for Medical Research (ASMR), Annual State Meeting, Curtin University – June 2011

Royce Ng, TICHR Institute presentation – June 2011

Royce Ng, TICHR Postgraduate forum – August 2011

Royce Ng, Australasian Society for Immunology, Annual State Meeting – October 2011

Royce Ng, Australasian Society for Immunology, Annual National Meeting, Adelaide - December 2011

Naomi Scott, Australian Society for Medical Research (ASMR), Annual State Meeting, Curtin University – June 2011

External Committees

PH Hart, Invited Member, NHMRC Academy

PH Hart, Invited Member, NHMRC RGMS working group.

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

PH Hart, President, Australasian Society for Dermatology Research

PH Hart, Chair, Organising Committee, Australasian Society for Dermatology Research Annual conference, Perth, May 2011.

LUNG GROWTH AND RESPIRATORY ENVIRONMENTAL HEALTH

Overview

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

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

The two key highlights of 2011 were the expansion of our research program to include studies specifically designed to assess environmental factors that may be contributing to the gap in health between indigenous and non-indigenous Australians (Collaborator: A/Prof Roz Walker, TICHR) and the development of a key collaboration with engineers from Monash University (Collaborator: Dr Fouras, Monash) examining novel imaging technologies for respiratory disease.

Early life determinants of lung growth

VITAMIN D DEFICIENCY AND LUNG GROWTH

Rachel Foong, Shelley Gorman, Prue Hart, Graeme Zosky

There has been a dramatic increase in recent decades in the prevalence of vitamin D deficiency in Australia and worldwide. Vitamin D deficiency is associated with a number of diseases including, 1) the bone disorder rickets (due to the importance of vitamin D in calcium homeostasis), 2) autoimmune disorders and 3) cardiovascular disease. Recent prominent publications have also implicated vitamin D in the pathogenesis of obstructive lung diseases such as asthma and COPD. Additionally, epidemiological studies have shown a strong association between serum vitamin D levels and lung function suggesting an important link between vitamin D status and lung health. However, there had been no study showing a direct lung between vitamin D deficiency and lung growth/structure/function. In 2010 we published a study in the leading respiratory journal (American Journal of Respiratory and Critical Care Medicine) on the lung structure and function of mice raised on vitamin D deficient and replete diets (established by Dr Gorman and Prof Hart). 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.

Funding: NHMRC, Asthma Foundation of W.A.

THE EFFECTS OF *IN UTERO* TOBACCO SMOKE EXPOSURE ON LUNG GROWTH AND HEALTH

Alexander Larcombe, Graeme Zosky, Rachel Foong, Peter Sly (UQ).

Unborn children exposed to tobacco smoke are more likely to suffer respiratory disorders such as bronchitis and wheeze and are more likely to be admitted to hospital for respiratory problems. Exposure to cigarette smoke before and directly after birth affect a child's lung function, however, a mother's smoking during pregnancy, rather than her smoking status after the birth is more highly correlated with the development of childhood asthma and wheeze. There is an association between *in utero* exposure to cigarette smoke to reduced lung function and childhood asthma, however the mechanisms for this are unknown.

This project began in 2008 when we characterized our commercially available cigarette smoking machine using adult mice. We showed that a regime of 3 cigarettes twice per day for 13 days was optimal for in utero cigarette smoke exposure studies.

Following characterization of the smoking machine, we began exposing groups of dams to mainstream cigarette smoke. Control dams were exposed to medical air only. When the resultant pups were two weeks old, we weighed them, measured their lung volumes, baseline lung function and lung mechanics over 20cm H2O inflation/deflation

manoeuvres and assessed lung morphometry. We showed that two week old mice exposed to cigarette smoke *in utero* were significantly smaller and had significantly lower lung volumes than control pups. As a result of their smaller size, cigarette exposed pups had significantly impaired lung function, although lung structure was not altered. These data were the first to show impaired lung function in mice exposed to tobacco smoke *in utero* using appropriate techniques.

Respiratory environmental health

ARSENIC INDUCED NON-MALIGNANT LUNG DISEASE

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

The contamination of groundwater with arsenic (As) is a global health problem. In the Ganges Delta (West Bengal, Bangladesh) over 80 million people have been exposed to unsafe levels of As from shallow tube wells that were installed to prevent the epidemic of waterborne diseases in infants. This exposure event is a public health catastrophe and has been described as the biggest mass poisoning in human history. Arsenic is a well recognised carcinogen and is listed by the International Agency for Research on Cancer (IARC) as a category 1 carcinogen. However, recent evidence from an exposure event in Chile has suggested that As is linked to the development of non-malignant obstructive lung disease. In particular, *in utero* exposure to As via drinking water has been linked to increased mortality due to bronchiectasis in young adults.

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

In 2011 we also completed a series of studies examine the effect of combining arsenic exposure with an additional respiratory insult using a mouse model of influenza infection. These data clearly demonstrate that arsenic can exacerbate influenza induced inflammation and alterations in lung function. These respiratory deficits also persisted into adulthood demonstrating the importance of early life environmental and viral exposures in determining adult lung health.

Funding: NHMRC Project Grant

REGIONAL ENVIRONMENTAL DETERMINANTS OF LUNG HEALTH

Graeme Zosky, Russell Wong, Robert Woodward (U.W.A.), Lucia Guiterrez (U.W.A.), Brian Devine (U.W.A.), Fiona Maley (U.W.A.), Angus Cook (U.W.A.)

Exposure to mining dust in towns close to open cut mines in Western Australia has been identified as a public health concern. In particular, children have been identified as a subgroup that is at high risk of respiratory disease as they are active close to the ground, have higher ventilation rates than adults and often play in areas (e.g. community playgrounds and outdoors) where dust levels are high. This study is the first to directly assess lung responses to inhaled "real world" particles from mining sites in Australia. We will determine whether exposure to dust in communities close to mines causes a level of inflammation in the lung that is of concern and also whether the response varies depending on the mineral/metal content of the dust. These studies will assist in informing public health and safety policy in these communities.

In 2010 we completed Phase 1 of the *in vivo* animal exposure studies associated with this project. In these studies adult BALB/c mice were exposed to varying (0, 10, 30, 100 µg) concentrations of PM_{10} (< 10 µm) collected from Newman and Kalgoorlie suspended in 50 µL of saline by intranasal inoculation under light anaesthesia. Mice were assessed for inflammatory responses in the lung 6, 12, 24 hrs and 7 days post inoculation. Additional groups of mice were exposed to 100 µg of 10 µm silica or inert polystyrene beads as controls for generic responses to inhaled particulate matter. To date we have completed the analysis of cell numbers (and type) from lavage samples from mice in all groups. The magnitude of the influx of inflammatory cells was dependent on the dose and sample used. The silica and polystyrene preparations resulted in a minor (barely detectable) inflammatory response. In contrast a significant influx of neutrophils (polymorphonucleocytes) was observed in the mice exposed to PM_{10} from both Kalgoorlie and Newman with a greater response in mice exposed to PM_{10} from the latter. We are currently measuring cytokine levels in lavage fluid from these mice and have begun Phase 2 which involves exposing mice to samples from other sites and measuring lung function at key timepoints (6 hr, 24 hr and 7 days post-inoculation).

In 2011 we extended this study to include particles obtained throughout W.A. including Tom Price, Port Hedland and Karratha. This study (data currently being analysed) is the first comprehensive examination of the potential respiratory health impacts of geogenic particles obtained directly from communities exposed to high dust loads. For the first time we hope to identify the key elements of these particles that have the greatest impact on respiratory health with a view to designed remediation programs in these communities.

Funding: CRC for Asthma

ENVIRONMENTAL HEALTH OF REMOTE INDIGENOUS COMMUNITIES

Graeme Zosky, Roz Walker

There is a significant gap in health between indigenous and non-indigenous Australians. This is particularly true for respiratory health and in individual 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 this disparity in respiratory health. We travelled to several communities of the Martu people in the eastern Pilbara and collected water and dust samples for analysis of heavy metal contamination. We are now expanding this program to conduct real-time monitoring of the inhalable dust with a view to estimating exposure levels in the community.

Funding: Thoracic Society of Australia and New Zealand (Rob Pierce)

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

Alexander Larcombe, Rachel Foong, Graeme Zosky

This ongoing project is designed to directly address the issue of whether acute exposure to diesel exhaust particles (DEP) results in exacerbation of existing respiratory illness. In 2009 and 2010 we established a mouse model of acute DEP exposure using intra-nasal instillation of DEP (ie small amounts of DEP in solution are placed on the nose of mice and inhaled). At a variety of time-points post exposure (ranging from 3 hours to 4 weeks) we took bronchoalvelar lavage fluid for assessment of inflammation and uptake of carbon black by alveolar macrophages. We identified significant cellular inflammation which peaked ~6 hours post exposure. We also measured increased levels of a number of cytokines including MIP-2 and MCP-1 post exposure. Cellular inflammation had largely resolved 48 hours post exposure. We also measured lung volume, baseline lung function and lung mechanics over 20cm H_2O inflation/deflation manoeuvres for these mice 6 and 24 hours post exposure. We noted impaired lung function at 6 hours, which had returned to normal after 24 hours. A significant component of this project was assessing uptake of DEP by alveolar macrophages. We measured a distinct bi-phasic uptake of DEP at levels comparable to those seen in children chronically exposed to soot / DEP, indicating the real-world relevance of these studies.

In 2011 we combined this DEP model with our established model of influenza infection and clearly demonstrated that DEP can enhance viral replication and exacerbate influenza induced inflammation. This observation has the potential to influence how people who are hospitalized with influenza are treated and to inform public health warnings on high pollution days.

Mechanisms of airway hyperreponsiveness in asthma

NOVEL IMAGING MODALITIES FOR THE ASSESSMENT OF REGIONAL AIRWAY CONTRICTION

Graeme Zosky, Andreas Fouras (Monash), Stuart Hooper (Monash)

In 2011 we established a collaboration with researchers at Monash University who are developing novel methods for imaging the lung using highly coherent synchrotron based radiation. These studies are conducted at the third generation synchrotron in Japan and are yielding novel insights into the regional effects of bronchoconstricting agents.

VIRAL INDUCED AIRWAY HYPERRESPONSIVENESS

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

These studies span a number of different projects and involve infecting mice with respiratory viruses (primarily rhinovirus and influenza) at different ages and under different conditions (e.g. in the presence of other respiratory insults). In 2010 we focused on 2 aspects; the role of neutrophil elastase in the progression of influenza induced airway hyperresponsivness (AHR) and the impact of diesel exhaust particle (DEP) exposure during acute influenza infection.

Neutrophil elastase; We have shown previously that influenza induced AHR is due to disruption of the epithelial barrier resulting in increased access of bronchocontrictor agents to the airway smooth muscle. Neutrophils are one of the primary response cells involved in the inflammatory response to influenza. Neutrophils release a number of key products including neutrophil elastase (NE) which, when in excess, can damage the lung tissue. We hypothesized that NE, by disrupting the epithelial barrier, was responsible for influenza induced AHR. To test this we used a genetically modified mouse which lacks neutrophil elastase (NE-/-). NE-/- mice and wild-type littermates were infected with influenza A and studied for inflammation, viral replication and lung function at the peak of the response (3-4 days post-infection). We found that there was no difference in responses between the two groups of mice suggesting that NE is not involved in the induction of influenza related AHR.

DEP and influenza; As part of our ongoing interest in respiratory responses to environmental exposures we have developed and characterized a mouse model of acute DEP exposure. DEP is one of the major contributors to atmospheric particulate matter in urban areas. There are strong epidemiological associations between levels of particulate matter in the atmosphere and respiratory morbidity and mortality. One explanation for this observation may be DEP induced exacerbation of respiratory disease. In order to test this we exposed mice infected with influenza, at the peak of inflammation (day 4), to DEP and measured responses 6 hours later. We found that mice exposed to both DEP and influenza had higher levels of inflammation compared to mice exposed to either DEP or influenza alone. Additionally, DEP exposure increased viral titre suggesting that it enhanced viral replication. These studies are ongoing and we plan to extend the measurement timepoints to determine whether DEP exposure prolongs the resolution of influenza symptoms.

Funding: UWA Research Development Award

EMERGING MODELS OF ASTHMA

Alexander Larcombe, Graeme Zosky, Peter Noble (KEMH)

Experimental mouse models of aeroallergen sensitization have helped advance our

understanding of respiratory diseases such as asthma. Traditional mouse models, however, have a number of inherent draw-backs and are far from the ideal model of human allergic airways disease. Typically, mouse models of "asthma" involve systemic sensitization of adult animals where allergen (usually ovalbumin, from chicken eggs) is used in conjunction with powerful chemicals to enhance the response. Whilst still an extremely valuable tool for the investigation of allergic airways disease in mice, this situation does not mimic the process in humans, which happens at an early age across the nasal mucosa. To address this, we have designed a project to validate and to further characterize two mouse models of house dust mite (HDM) sensitization and by this assess the impacts of such sensitization/ exposure on respiratory health. Mouse models of HDM exposure have strong links to human allergic airways disease and are potentially a considerable improvement on other mouse models. This is because HDM, unlike ovalbumin, is a cosmopolitan guest in human habitation, and naturally causes allergic airways disease in humans. Unlike earlier studies by other researchers, we will use an array of specialised in-house techniques suitable for measurement of lung function in mice, allowing us to reveal important physiological effects of HDM that may have been previously overlooked.

To date, we have exposed adult BALB/c mice to 25µg HDM protein in saline daily for ten sequential days. Control mice received saline only. The mice receive the HDM intranasally, mimicking the route of exposure in humans. We then measured lung volume, baseline lung mechanics and hyperresponsiveness to methacholine 24, 48 and 72 hours post the final exposure. We have shown significant impacts on lung function, including airway hyperresponsiveness for HDM exposed mice. The impacts were greatest 24 hours after the final exposure. We also took blood and bronchoalveolar fluid from these mice for analysis of total IgE and cellular inflammation. These mice showed significantly increased total IgE and eosinophilia, two key features of allergic airways disease.

One of the most striking abnormalities in patients with obstructive lung disease is a loss of the bronchodilation that normally occurs in healthy individuals when they take a deep inspiration (deep inflation, DI). In both asthma and COPD, the protective action of DI fails. It is argued that an impaired response to DI is intimately related to disease morbidity including airway obstruction and airway hyperresponsiveness (AHR). The general aim of this on-going project is to examine the underlying mechanisms governing beneficial responses to DI and to determine the susceptibility of the system to interference in disease. In 2011 we demonstrated the capacity for a DI to modify both the timing (rate) and magnitude of constriction following exposure to the bronchoconstrictor MCh.

Staff and Students

HEAD OF GROUP

Graeme R Zosky PhD MBiostat
Principal Investigator, Telethon Institute for Child Health Research
Associate Professor, Centre for Child Health Research, The University of Western Australia

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Russell Wong BSc(Hons)

Luke Berry BSc

Dr Peter Noble PhD (Honorary member)

POSTGRADUATE STUDENTS

Rachel Foong BSc(Hons) PhD Candidate

Kathryn Ramsey BSc(Hons) PhD Candidate

RESEARCH SUPPORT

Marina Stubbs

Awards

Kathryn Ramsey, Maurice Blackburn International Travel Award

Kathryn Ramsey, Lung Institute of Western Australia Junior Medical Scientist Award

Kathryn Ramsey, Australia Society for Medical Research (W.A.) Murdoch Award

Kathryn Ramsey, Thoracic Society of Australia and New Zealand Travel Award

Rachel Foong, Thoracic Society of Australia and New Zealand Travel Award

Catherine Boylen, Thoracic Society of Australia and New Zealand Travel Award

External Committees

LOCAL

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

Graeme Zosky. Thoracic Society of Australia & New Zealand ASM Organising Committee.

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

Kathryn Ramsey. Thoracic Society of Australia & New Zealand ASM Organising Committee.

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

Invited Presentations

Graeme Zosky. Australian Physiological Society Conference 2011. "Alterations in lung structure can perpetuate inflammation leading to chronic lung disease"

ACTIVE collaborations

Assoc Prof Angus Cook, University of Western Australia

Prof Alan James, Sir Charles Gairdner Hospital, W.A.

Prof Zoltan Hantos, University of Szeged, Hungary

Prof Peter Sly, University of Queensland, QLD

Prof Steve Stick, Princess Margaret Hospital, W.A.

Dr Andrea Hinwood, Edith Cowan University, W.A.

Dr Andreas Fouras (Monash)

Professor Stuart Hooper (Monash)

Dr Ben Mullins, Curtin University

MOLECULAR BIOTECHNOLOGY

Overview

Childhood respiratory infections: Immune responses to childhood respiratory infections have become a major subject of investigation by the Division of Molecular Biotechnology. This follows from the finding that nearly all infants that become allergic to inhalant allergens show developmental delays in the production of antibodies to common colonising bacteria, and that when the low responses persist, the children have a high propensity to develop asthma. Indeed children with the worst asthma have the lowest anti-bacterial responses, along with a poor IgE/IgG profile for their responses to allergens. These discoveries were dependent on the development of recombinant and highly purified antigens so defined reproducible observations can be made and the development of methods for absolute quantitation. To date the emphasis has been to establish the reproducibility of the findings in different cohorts of children, with different antigens and with antigens from different bacteria, *Haemophilus influenzae* and *Streptococcus pneumoniae*. Not only have the associations with the low IgG1 responses been reproduced but so has the unusual association of reduced risk of asthma with IgE antibody production to bacterial proteins. The mechanisms responsible for these effects are now being explored.

Rhinovirus infection: There has been increasing recognition that rhinovirus infection is not only found frequently in exacerbations of asthma but that children who become asthmatic have more frequent rhinovirus infections. It is proposed that serological studies will be able to show if the increased infection is associated with lower antibody titres to the virus and hence an immunological insufficiency or if there are increased titres that might be expected from increased infection, for example due to increased exposure. Antibody titres can also show the prevalence of infection from the three species of rhinovirus, HRV-A, B and C, and might provide a diagnostic method for identifying recent infection associated with a clinical episode. The production of structurally authenticated recombinant proteins for major VP1capsid antigens has now been accomplished and pilot studies have already show the interesting result that antibodies to HRV-C are found infrequently in adults.

Allergens of the house dust mite: The measurement of IgE antibody titres to Der p 15 and Der p 18, allergens expected to bind chitin, has demonstrated that immune responses to different house dust mite allergens are regulated by different pathways. The IgE titres to these allergens correlated strongly with each other but not to responses to other house dust mite allergens. These form a separated group that correlate with each other. The results emphasise the need to investigate immune responses to different house dust mite allergens separately and not with extracts.

Molecular Biotechnology

DEVELOPMENT OF ANTI-BACTERIAL IGG AND IGE ANTIBODY IN HOUSE DUST MITE ALLERGIC CHILDREN

B. J. Hales, L. Y. Chai, C. E. Elliot L. A. Hazell, W-A Smith, T. K. Heinrich, W. R. Thomas with M.M.H. Kusel, P. D. Sly and P. G. Holt from Cell Biology and Clinical Sciences

A preschool (CAS) cohort was used to study antibody responses to the P4 and P6 antigens from *Haemophilus influenzae* and Psp-A and Psp-C antigens of *Streptococcus pneumoniae*. Children that became allergic to house dust mite allergens had a delayed development of IgG1 responses to all the bacterial antigens examined and, especially for the *H. influenzae* allergens, children who became asthmatic (judged at 5 years) had early and persistent low IgG1 titres. The same was found for *S. pneumoniae* but not to the same degree. This corroborates the results from a previous emergency room study. The unusual association of IgE antibody and low risk for asthma was found in 5 year old children corroborating results from an older aged cohort. There was additionally an inverse association between IgE anti-house dust mite allergen titres and IgE anti-P6 bacterial protein, which indicates protection from allergic sensitisation, is part of the mechanism. The size of the anti-bacterial IgE and the anti-bacterial IgG1 titres were correlated indicating they are part of the same mechanism or markers for the same mechanism that is now being investigated.

RHINOVIRUS ANTIGENS AND ANTIBODIES

J. Iwasaki, W. Smith, W. R. Thomas, C. E. Elliot, LY Chai, L. A. Hazell, B. J. Hales

The VP1 proteins are the most antigenic capsid antigens of the type A, B and C species of human rhinovirus. Each has about 80% sequence identity within the species but only 20% between species, which would not be expected to cross react. The type C is a newly identified species that has been especially associated with lower respiratory tract infection and asthma in children. *In vitro* cultivation of the type C is difficult so the production of the recombinant polypeptide is the only avenue available to produce antigens to measure immune responses and conduct seroepidemiology. DNA encoding the two representative VP1 antigens from each species has been obtained by gene synthesis and expressed as recombinant proteins by several strategies. Recombinant VP1 assembled as a discrete multimer has been produced and purified by several chromatographic steps. It is by circular dichroism highly structured with the beta-sheets expected from the natural antigen. Pilot studies with adults show that in contrast to the type A VP1 protein only a few individuals have high titres of antibodies binding to type C. It may therefore only be a paediatric infection or the observations made by PCR-based virus detection from hospitalised children may have overestimated the prevalence in the community.

DER P 15 AND 18 AND INDEPENDENT REGULATION OF IGE RESPONSES TO DIFFERENT GROUPS OF HOUSE DUST MITE ALLERGENS

W. Smith, C, E. Elliot, L. Y. Chai, L. A. Hazell, B. J. Hales, W. R. Thomas with S. Stone from Drug Discovery and S. Piboonpocanun, T. Tipayanon and S. Thanyaratsrisakul, Mahidol University, Bangkok

Der p 15 and Der p 18 which are respectively a chitinase-like protein and a chitin binding domain protein were produced in the yeast *Pichia pastoris*. From their molecular size they were glycosylated to a similar level to the natural allergens that included the extensive glycosylation of Der p 15. Circular

dichroism revealed a high degree of secondary structure with the expected amount of beta sheet and alpha helix demonstrated for the family 18 hydrolases homologous to Der p 15. IgE binding with adults showed that antibodies were restricted to subjects that had anti-Der p 1 and 2 antibodies but that the titres to Der p 15 and 18 correlated with each other but not to Der p 1 or Der p 2. They also did not correlate with responses to the Der p 5 and 7 allergens, which correlate with each other and Der p 1 and 2. Since Der p 15 and 18, which only have 29% sequence identity, do not cross react the results show a coordinated regulation of responses to these allergens that is different to the coordinated regulation of Der p 1, 2, 5 and 7. The regulation of IgE responses to allergens therefore depends on the allergen and not just to host factors or on non-specific adjuvant activity associated with the source of the allergen.

CD23 BINDING ASSAY IN CAT ALLERGY

L. Y. Chai, C. E. Elliot, T. K. Heinrich, W. R. Thomas and B. J. Hales

The ability of complexes of IgE antibodies and allergen to bind to the low affinity CD23 IgE receptor was studied. The extracellular portion of human CD23 was produced as a recombinant polypeptide fused to a coiled coil leucine zipper that promotes the formation of trimers, similar to how they are found in found in nature. The CD23 was isolated by size exclusion chromatography as a trimer and coated onto microtitre wells and used to capture IgE immune complexes produced by the incubation of allergen and sera from allergic subjects. The binding was read out with anti-IgE antibodies in a dissociation enhanced lanthanide fluoroimmunoassay (DELFIA). Studies with the Fel d 1 allergen showed that the IgE binding was only detected when both the IgE antibody and allergen were present and there was no binding when IgE was depleted with IgE receptor transfected RBL cells. IgG depletion in contrast increased the CD23 binding titre. Mouse CD23 did not bind human IgE-allergen complexes showing the expected species specificity.

Invited Presentations

W. R. Thomas. Guest workshop speaker. American Academy of Allergy Clinical Immunology, Dust mite allergens. Molecular mimicry of lipopolysaccharide-binding proteins and allergic sensitization. San Francisco, USA

External Committees.

W. R. Thomas. IUIS-WHO International Allergen Nomenclature Committee

W. R. Thomas. World Allergy Organization Committee on Aeroallergens

PAEDIATRIC RESPIRATORY PHYSIOLOGY

Overview

The Paediatric Respiratory Physiology research group was established in mid 2010 with the appointment of A/Prof Graham Hall by the Telethon Institute of Child Health Research. The primary aim of the group is the assessment of lung growth and development in both health and in respiratory disease, including asthma, cystic fibrosis and chronic lung disease of prematurity.

Cystic Fibrosis

EVOLUTION OF AIRWAY FUNCTION AND INFLAMMATION IN EARLY CF LUNG DISEASE

Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Shannon Simpson and Karla Logie 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 highlighting this as a crucial period for intensive and new treatments to prevent progression or even reverse lung disease. However, the evolution of peripheral airway pathology in early infancy is poorly understood and ongoing relationships between peripheral respiratory function and measurements of pulmonary inflammation or infection remain unknown. We hypothesise that infants with cystic fibrosis will demonstrate abnormal peripheral lung function manifested as altered lung parenchymal mechanics as assessed by the low-frequency forced oscillation technique (LFOT) and by ventilation inhomogeneities as determined using multiple breath washout (MBW). Further, we hypothesise that those infants with increased pulmonary inflammation will have correspondingly poorer peripheral respiratory function. The goals of this study are to evaluate these established standardised, 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.

Funded by NHMRC, USA Cystic Fibrosis Foundation

Indoor air pollution and lung health

IMPACT OF EXPOSURE TO AIR POLLUTANTS DURING THE PRENATAL PERIOD ON LUNG FUNCTION IN INFANCY

Graham Hall, Peter Franklin, Zoltan Hantos and Mark Tan 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

In 2011 we continued to recruit for this project with ~80% of eligible (non-smoking) pregnant women agreeing to participate. Ongoing research is aimed at integrating the assessments of air pollution during pregnancy and lung function measures in infancy.

Funded by NHMRC

Long term outcomes following preterm birth

CHARACTERISING RESPIRATORY HEALTH OF YOUNG CHILDREN BORN PRETERM

Graham Hall, Maureen Verheggen, Andrew Wilson, Stephen Stick, Jane Pillow

Advances in neonatal care have resulted in the survival of increasingly premature infants and changed the clinical presentation of bronchopulmonary dysplasia (BPD). The long-term respiratory outlook for young children born premature is not known. We aimed to characterize the lung function of young children born preterm in the surfactant era, who are now aged between 4 and 7 years by measuring lung function using Forced Oscillation Technique, Multiple Breath Washout, Diffusing Capacity, and Spirometry. We found children born preterm have worse lung function than healthy controls and that lung function worsened with increasing severity of disease. Symptom prevalence was similar in preterm children irrespective of BPD status. These results suggest that children born preterm have distal lung abnormalities which are more severe and sensitive to respiratory symptoms in those with BPD.

Funded by: Princess Margaret Hospital Foundation

INVESTIGATION OF THE INFLUENCE PRETERM BIRTH ON LUNG STRUCTURE AND FUNCTION IN SCHOOL AGE CHILDREN

Graham Hall, Andrew Wilson, Jane Pillow, Andrew Maiorana, Shannon Simpson, Karla Logie.

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of premature birth. Contemporary BPD is dominated by peripheral lung abnormalities including failed alveolarisation with a decreased number of large and simplified alveoli and abnormal pulmonary vascular development. The few studies to examine the long term respiratory outcomes in new BPD have demonstrated impaired gas transfer reduced cardiopulmonary exercise capacity, gas trapping and increased respiratory morbidity. None of these studies undertook a comprehensive assessment of lung structure, peripheral lung function and respiratory morbidity and examined the influence of neonatal history on the long term outcomes of new BPD. Studies of this nature are essential and will provide an improved understanding of the pathology of new BPD and its long term outcomes and allow a more targeted approached to the treatment and management of infants with BPD through the neonatal period and into childhood. The aims of this project are to:

- obtain novel information regarding lung structure in preterm children

with and without a history of new bronchopulmonary dysplasia BPD using HRCT scanning of the chest.

- assess peripheral lung function using tests sensitive to the pathophysiological changes encountered in children with BPD
- determine the response to a maximal cardiopulmonary exercise test (CPET) in children with and without BPD.
- assess the importance of the relative effects of prematurity, neonatal lung disease and other perinatal factors on alterations in lung structure, function and respiratory morbidity.

Key findings in 2011 were that

- All preterm children have abnormal lung structure, irrespective of the presence of BPD.
- Children with a history of BPD are twice a likely to exhibit exercise flow limitation when compared to preterm children without BPD.
- Respiratory symptoms such as wheeze and shortness of breath with exercise are significantly increased in children born preterm.

Funded by NHMRC, Raine Foundation and Princess Margaret Hospital Foundation

Asthma

CHARACTERISING OBJECTIVE LUNG FUNCTION IN YOUNG CHILDREN WITH RECURRENT WHEEZE

Graham Hall, Andrew Wilson, Stephen Stick, Shannon Simpson, Afaf Al Bloushi

Summary: Asthma results in episodic wheezing and is associated with cough and shortness of breath. In the majority of cases of persistent asthma, symptoms begin in early life with longitudinal studies suggesting that ~40% of children who wheeze in the first 3 years of life were still wheezing at 6 years. Patterns of wheeze prevalence and lung function are established by 6 years and do not change significantly by age 16. The pre-school years are therefore the time in which the most important alterations in lung function develop in susceptible individuals. In most asthmatics airway obstruction and its reversibility are quantified using spirometry. However spirometry requires considerable patient coordination and is not feasible for widespread use in young children. Lung function techniques, such as the forced oscillation technique (FOT) do not require active cooperation and are ideal for use in young children The use of these techniques to assess lung function in young children with recurrent wheeze may have major implications for our understanding of asthma pathophysiology in this age group. This study is investigating the influence of respiratory history and symptoms on lung function and bronchodilator responsiveness (BDR) in young children using the FOT and MBW techniques.

Staff and Students

HEAD OF DIVISION

Graham L. Hall; BAppSci, PhD, CRFS, FANZSRS
Associate Professor (Adjunct), Centre for Child Health Research, University of Western Australia
Associate Professor (Adjunct), Faculty of Health Sciences, Curtin University
Senior Respiratory Scientist in Charge, Respiratory Medicine, Princess Margaret Hospital

RESEARCH STAFF

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

Ms Judy Park BSc MBiostat

Dr Shannon Simpson PhD – Research Officer

Ms Maureen Verheggen M Med Sci – Senior Respiratory Scientist

Dr Andrew Wilson Paediatric Respiratory Physician

Ms Georgia L Banton BSc – Research Assistant

POSTGRADUATE STUDENTS

Ms Afaf Al Bloushi BSc PhD Candidate

Ms Karla M Logie BSc(Hons) PhD Candidate

Mr Chris O'Dea PhD, B. Med Sci (Resp Hsci) Hons

Mr Mark Tan MSc PhD Candidate

Mr Tim Rosenow BSc Grad Cert Paed Resp Sci – Honors Student

Theses passed

Maureen Verheggen; Master of Medical Science "Respiratory outcomes in young children born preterm in the surfactant area"

Awards

Graham Hall, Telethon Institute for Child Health Research PhD Supervisor of the Year

Chris O'Dea, "Excellence in respiratory measurements" at ANZSRS ASM

Chris O'Dea, Curtin Award at ASMR WA annual symposium

Shannon Simpson, European Respiratory Society Young Scientist Fellowship

Shannon Simpson, Ian Potter Foundation Travel Grant

Shannon Simpson, Australasian Cystic Fibrosis Conference; Best Poster Award

Maureen Verheggen, Maddison Scholarship

Maureen Verheggen, WA Respiratory Science Travel Award

External Committees

INTERNATIONAL

Graham Hall, Joint American Thoracic Society - European Respiratory Society Working Party on Infant Lung Function Testing (2003-)

Graham Hall, European Respiratory Society Global Lung Initiative Task Force: Co-Chair (2008 -)

Graham Hall, Joint American Thoracic Society -

European Respiratory Society Task Force for Provocation testing guidelines (2010 -)

Graham Hall, European Respiratory Society Annual Congress Paediatric Respiratory Physiology Abstract review committee

Graham Hall, Editorial Board; Respirology (Jun 2011 – Ongoing)

Graham Hall, Editorial Advisory Panel; Expert Review of Respiratory Medicine (Oct 2006 – Ongoing)

NATIONAL

Graham Hall, Thoracic Society of Australia and New Zealand Professional Standards Sub-committee (2008 -)

Graham Hall, Thoracic Society of Australia and New Zealand Paediatric Special Interest Group: Convenor (2007 – Mar 2011)

LOCAL

Graham Hall, Western Australian Health Department: Health Professions Strategic Reference Group (2007 -)

Graham Hall, Asthma Foundation of Western Australia Board member (2010 –)

Invited Presentations

Graham Hall, ANZSRS Progression of Cystic fibrosis lung disease mini-symposium: "Respiratory physiology and Cystic Fibrosis lung health: Which test for what age?"

Graham Hall, ATS Workshop: Evaluation of respiratory mechanics and function in the ICU "Respiratory Mechanics in the ventilated child: The role of the forced oscillation technique"

ACTIVE collaborations

Royal Perth Hospital, Respiratory Medicine, Perth - Dr Kevin Gain

King Edward Memorial Hospital, Neonatology, Perth - Prof Jane Pillow, Assoc Prof Noel French and Dr R Hagan, Dr Mary Sharp

University of Western Australia, Perth - A/Prof Dr Peter Franklin, A/Prof Sunalene Devadason

Royal Children's Hospital, Melbourne - Dr Sarath Ranganathan

University Children Hospital, Zurich Switzerland - Dr Alex Moeller

University Children Hospital, Vienna Austria - Dr Fritz Horak

Institute for Child Health, London UK - Prof Janet Stocks

University of Szeged, Hungary - Prof Zoltan Hantos

Erasmus University, Rotterdam, The Netherlands - Prof Philip Quanjer

POPULATION SCIENCES

Overview

The Division of Population Sciences is the largest Division within the Telethon Institute. The Division conducts a wide range of research with a focus on multidisciplinary studies in the areas of developmental disorders, nutrition, indigenous health, developmental health, childhood cancers, services for children and families, and mental health.

The Division has a staffing mix of around 200 staff and students that include a wide range of different research specialists including epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists. The Division has a focus on collaboration in particular with government agencies as a means of translating the results of our research into policy and practice where it can make a real difference to the lives of Western Australians.

The Division prides itself on the breadth of research methods utilized across our research groups. Our quantitative researchers use mathematical modelling and other biostatistical techniques to identify patterns and trends in child health. They may be working with databases that have thousands and thousands of records collected over decades. Our qualitative researchers will utilise mixed methods including focus groups, one on one interviewing and participatory action research techniques to explore the opinions, perceptions and views of parents and families on a variety of issues.

The Division's commitment to prevention and early intervention is seen by our collaborative working relationships with government and community partners with the overall aim of ensuring that Western Australian's children are happy and healthy. This means that Western Australian families are supported to enable their children to achieve an optimal level of social, emotional, academic, and vocational wellbeing.

HIGHLIGHTS FOR 2011

In February, researchers from the Division uncovered more evidence for a link between early testosterone levels and autism. The study used data from the long-running Raine Study to examine the relationship between autism-like behaviours in early childhood among otherwise typically developing girls and the timing of their first period. The research found that girls with autism-like symptoms such as poor eye contact and repetitive behaviours were older at the time of their first period. These findings suggest a common developmental mechanism underlying both autism and the later onset of puberty. This study is in line with previous findings by researchers within the Division which has shown a positive association between concentrations of testosterone taken from umbilical cord blood and autism-like symptoms in 10 year old children.

Also in February, research from the Division showed that the Western Australian pneumococcal vaccine program has contributed to closing of the gap in serious infections in Aboriginal children. This study found that hospitalizations for pneumonia across Western Australia have declined in Aboriginal children while rates for non-Aboriginal children have remained the same. Pneumonia is a serious illness and a common reason for children to be admitted to hospital. Around one-fifth of childhood deaths globally – approximately 2 million per year – are due to pneumonia. The research team supports the continued monitoring of pneumonia trends in high-risk populations to fully understand the impact of pneumococcal vaccination and other public health interventions.

In April, the results of the Australian Early Development Index (AEDI) were released. Researchers within the Division have played an integral role in the planning and delivery of the AEDI in collaboration with the Australian Government and State and Territory Governments and working in partnership with the Centre for Community Child Health at Murdoch Children's Hospital. The AEDI results report on 261,147 children (97.5 per cent of the estimated five year old population) throughout Australia from data collected during their first year of school in 2009 to provide a snapshot of children's health and development in different communities. The AEDI results provide communities with rich information about how their young children are developing. This information can be used to encourage parents, families and leaders to come together and focus on specific things that can be done to enrich and extend developmental opportunities and expectations for families and children that are doing less well than others.

Also in April, researchers from the Division found a link between the number of stressful events experienced during pregnancy and increased risk of behavioural problems in children. Common stressful events included financial and relationship problems, difficult pregnancy, job loss and issues with other children while major life stressors were events such as a death in the family. This study found that the overall number of stresses is most related to child behaviour outcomes. Two or fewer stresses during pregnancy are not associated with poor child behavioural development, but as the number of stresses increase to three or more, then the risks of more difficult child behaviour increase. What this study says is that we as a community need to target pregnant women with support programs to ensure stress does not negatively affect their unborn child.

In July, a new study from the Division showed that late-talking toddlers are no more likely to experience behavioural and emotional difficulties during childhood and adolescence than children who have normal language development. Dr Whitehouse said the results offer reassurance to parents of late-talkers that their language delay is not in itself a risk factor for later behavioural and emotional problems. The findings of this study suggest that parents should not be overly concerned that their late-talking toddler will have language and psychological difficulties later in childhood.

Also in July, researchers from the Division showed that parents have an important role to play in teaching their children to understand another person's feelings and point of view. The study found that mothers who have higher levels of empathy were more likely to encourage their children to think how others might be feeling, which in turn was associated with greater development of empathy skills in

the child. What this means is that children with more advanced perspective-taking skills behave more positively with other people. The study reinforces the importance of parents in modelling good social behaviour in early childhood. It supports previous research that found that warm and responsive parenting in infancy also promotes the development of prosocial behaviour.

In October, a study within the Division found a link between traffic emissions and reduced fetal growth. The study showed that a neonate who would have otherwise attained an optimal birth weight of 3.5 kg would be expected to be born 58 g lighter. The results reflect about half of the effect observed for maternal smoking during pregnancy among this group. These results were surprising because these effects were observed when air quality guidelines met national standards.

Also in October researchers from the Division found that babies born by elective caesarean are more likely to be admitted to hospital with the serious respiratory infection, bronchiolitis, in the first year of life. Although the effect was relatively modest, it is the first study to link elective caesareans to bronchiolitis. Bronchiolitis, generally caused by the common respiratory syncytial virus (RSV), is one of the most common reasons for babies to be admitted to hospital. Bronchiolitis also has been shown to be associated with an increased risk of asthma in children. This study has implications to the rising caesarean rates in Australia and this potential impact on the immune system might be another factor that parents and doctors may consider if choosing a caesarean for other than medical reasons.

In November, a study by Divisional researchers found more evidence that reading books to young children and helping them visually to follow the story improves a child's language. The study investigated the factors that facilitate children's language (vocabulary) development between 9 and 34 months of age using data from *Growing Up in Australia: the Longitudinal Study of Australian Children (LSAC)*. The study found that higher levels of parent-child book reading are associated with significantly better child language (vocabulary) development. Also children with more educated mothers have larger vocabularies because they engage in more parent-child book reading. The study also confirmed previous research demonstrating a gender gap favouring girls, who had a significantly greater vocabulary than boys at around 3 years of age.

Finally, a study released in December found that rates of child maltreatment over the last two decades in developed countries has not consistently decreased despite a raft of policy initiatives. The study used three types of indicators of child maltreatment - violent deaths in children, injuries related to maltreatment and involvement by child protection agencies, and compared these across different countries. The study found large variations between countries in the frequency of involvement by child protection agencies, but much less variation in rates of maltreatment-related injury or violent death, reflecting differences in government policies. It also found that violent deaths in the USA were more than five times higher than in Australia, which together with Sweden had the lowest rates. There was little variation between countries in the rate of maltreatment related injury admissions and officially recognised physical abuse or neglect. New Zealand and USA has substantially higher child protection investigations while placement in out of home care was ten times higher in Manitoba, Canada than in other countries, and twice as high for infants in England, New Zealand and the USA than in WA or Sweden. This research reinforces the need to improve the evidence base for child protection policies.

Air pollution

THE INFLUENCE OF AMBIENT AIR POLLUTION FROM TRAFFIC EMISSIONS AND PREGNANCY OUTCOMES

Gavin Pereira (ICHR), Angus Cook (UWA), Natasha Nassar (USyd), Carol Bower (TICHR), Nick de Klerk (TICHR), Phillip Weinstein (UniSA), Eve Blair (TICHR), Fatima Haggar (Ottawa Hospital, Canada).

International research and animal studies indicate the potential for adverse effects of traffic emissions on various pregnancy outcomes, as summarised in our review article published in the journal *Surveys and Perspectives Integrating Environment and Society* (2010). A statistical model for ambient air pollution (criteria pollutants) was developed and peer-reviewed as a full paper through submission to the *International Clean Air and Environment Conference* (2009).

This exposure model was then "tested" by application to a study on asthma emergency department presentations, published in the *Medical Journal of Australia* (2010). Exposure to traffic-related air pollution was associated with increases in emergency department presentations, and the observed effects were considerably greater than previously reported in Australia. A new method to generate a map of disease risk was also developed and published in *Health and Place* (2009). The impact of geographic variation of socioeconomic status using these maps, which was peer reviewed as a full paper at the *State of Australian Cities Conference* (2009).

We examined whether proxies, such as traffic counts, were appropriate substitutes for direct measurement of air pollutants but found that this was not the case; *International Journal of Health Geographics* (2009). Consequently, funding was obtained from the CRC for Asthma and Airways and passive air sampling (nitrogen dioxide) was undertaken throughout the Perth metropolitan area in 2010. During this period of field work, a computer model (dispersion model) for traffic emission exposure was applied to investigate fetal growth restriction among a small population. We found that traffic-related air pollution (carbon monoxide) was associated with restricted fetal growth, although the effects were limited to one of the three study areas; *Australian and New Zealand Journal of Public Health* (2011). A study on the seasonal variation in fetal growth was also conducted to distinguish whether the variation in growth was due to pollutants or weather, and found that fetal growth restriction

was associated with higher temperatures, independently of pollution; *American Journal of Obstetrics and Gynecology* (2011). At the completion of the field work, a exposure model was developed using field measurements of a marker for traffic emissions (nitrogen dioxide), traffic counts, temperature and a range of other inputs. The papers reporting the effects of this exposure on fetal growth, preeclampsia and stillbirth are currently under review. To summarise these studies, we observed strong support for (i) a weak effect of traffic-related air pollution on fetal growth, (ii) a weak effect on risk of preeclampsia, and (iii) a strong effect on stillbirth.

We also conducted a study to validate a measure used to assess fetal growth using serial ultrasound scans from the RAINE cohort (under review).

The findings of these studies were presented at national and international conferences, including: the Conference of the Royal Society of Public Health (London, 2011), the Conference of the International Society of Environmental Epidemiology (Barcelona, 2011), the Annual Meeting of the Australasian Epidemiology Association (Sydney 2010, Perth 2011), the Annual Meeting of the CRC for Asthma and Airways (Sydney 2010), the Pacific Basin Consortium Conference (Perth, 2009) and the Australia-China Biomedical Research Conference (Tianjin China, 2009).

Funders of the project: Australian Postgraduate Award, University Postgraduate Award, Perron award, CRC for Asthma and Airways award, Australia China Society for Biomedical Research award, Commercialisation Training Scheme award, UWA GRST grant

Birth Defects and Developmental Disorders

ALCOHOL AND PREGNANCY:

In the late 1960's researchers in France and the US were documenting the development of children born to alcoholic mothers. Dr Kenneth Lyons and Dr David Weyhe Smith from the University of Washington Medical School identified a pattern of facial, limb and cardiovascular defects in 1973 and called it Fetal Alcohol Syndrome (FAS). Over time research has identified a range of effects (including physical, behavioural and cognitive) that can arise from prenatal alcohol exposure. The term Fetal Alcohol Spectrum Disorders (FASD) has developed to include FAS as well as other conditions resulting from prenatal alcohol exposure. The first studies of FAS in Australia were published between 1978 and 1983. The Alcohol and Pregnancy team at the Telethon Institute has been at the forefront of research and involvement in the translation into policy and practice. Between 2000 and 2011 Telethon Institute researchers have been authors on 46 published papers on alcohol and pregnancy. As part of our aspiration to provide information on alcohol and pregnancy a new website was launched in 2011. The website includes general information on alcohol and pregnancy in addition to the following: current Telethon Institute projects on FASD; previous projects; contributions to policy and practice; other alcohol and pregnancy projects in Australia; alcohol and pregnancy publications involving Telethon Institute researchers; resources; community participation; alcohol guidelines; living with a child with a FASD; where to go for assistance and links to sources of Australian and international information for parents/carers, health professionals, workers in health, education and justice sectors, politicians and researchers. The Alcohol, Pregnancy and FASD website can be viewed at http://alcoholpregnancy.childhealthresearch.org.au.

In 2011 submissions were made to the House of Representatives Standing Committee on Social Policy and Legal Affairs Inquiry into Foetal Alcohol Spectrum Disorder and the Western Australian Government Health Standing Committee Inquiry into improving educational outcomes for Western Australians of all ages (specifically item 5 *Fetal Alcohol Syndrome: prevalence, prevention, identification, funding and treatment to improve education, social and economic outcomes*).

A highlight of 2011 was the introduction of the Social Security and Other Legislation Amendment (Miscellaneous Measures) Bill into the Federal Parliament. This Bill called for the Parliament to continue to facilitate and support the development of a FASD national diagnostic tool for use by medical professionals and other health service providers, to give FASD the status of a recognised disability in Australia, and to institute a national awareness campaign, among other calls. FASD is currently not recognised as a disability by the Australian Government.

ALCOHOL AND PREGNANCY: EDUCATIONAL RESOURCES FOR HEALTH PROFESSIONALS

Jan Payne, Carol Bower, Kathryn France, Nadine Henley, Heather D'Antoine, Anne Bartu, Colleen O'Leary, Elizabeth Elliott, Elizabeth Geelhoed, Lynda Blum, Roslyn Giglia, Janet Hammill, Ray James (dec'd), Christine Jeffries-Stokes, Anne Mahony, Daniel McAullay, Anne McKenzie, Raewyn Mutch.

The Alcohol and Pregnancy Project (2006-2008) provided educational resources for Western Australian (WA) health professionals to inform them about the prevention of prenatal alcohol exposure and Fetal Alcohol Spectrum Disorder (FASD). Studies conducted in WA in 2002 and 2004 showed that WA health professionals were poorly informed about alcohol consumption in pregnancy and Fetal Alcohol Syndrome (FAS). The majority of these health professionals requested educational resources for themselves and information to give to clients. These results led to the formation of the Alcohol and Pregnancy Project.

We developed educational resources for WA health professionals using formative research. We used project management and incorporated consumer and community representatives' expertise into all aspects of the project. In 2007, the educational resources were distributed to 3,348 health professionals (Aboriginal health workers, allied health professionals, community nurses, general practitioners and obstetricians), and to 159 paediatricians. Six months later, we surveyed 1,483 health professionals and 133 paediatricians. We compared health professionals' responses

with results from 2002 and paediatricians' with results from 2004 using prevalence rate ratios and 95% confidence intervals. At the end of the project we conducted a survey to evaluate researchers' (n=16) and consumer and community representatives' (n=13) perceptions of the process, context and impact of consumer and community participation in the project. We also conducted a post-project review of researchers' (n=16) opinions on project management and whether it made a difference to the project.

The response fraction for health professionals was 67.7%. Of these, 69.8% had seen the educational resources and of these, 77.1 % had used them. Comparing results from 2002 with 2007, there was a 35% increase in the proportion who knew all the essential features of FAS and there was a 52% increase in the proportion who had diagnosed FAS. There was no increase in the proportion who routinely asked about alcohol consumption, but there was a 31% increase in the proportion that routinely provided information about the consequences of alcohol consumption in pregnancy. The response fraction for paediatricians was 61.7%. Of these, 65.9% had seen the educational resources and of these, 66.7% had used them. Comparing results from 2004 with 2007, there was no increase in the proportion who knew all the essential features of FAS or who had diagnosed FAS, and no increase in the proportion who routinely asked about alcohol consumption when taking a pregnancy history. There was a 93% increase in the proportion that provided information on the consequences of alcohol consumption in pregnancy (based on very small numbers). Fifteen researchers (93.8%) and seven (53.8%) consumer and community representatives completed an evaluation questionnaire and both thought that consumer and community participation had significant influence on the success of project outputs and outcomes. Fifteen researchers (93.8%) completed a post-project review and reported that project management increased the effectiveness of the project, communication, teamwork, and application of researchers' expertise. The evaluation of the project showed that although the measure of effect was not large, the extent of change has public health significance because the reach was extensive.

Following the distribution of the educational resources to WA health professionals, we demonstrated some improvement in their knowledge, attitudes and practice in relation to alcohol consumption in pregnancy and FAS. FASD is a serious public health problem. The educational resources have potential to increase health professionals' capacity to reduce prenatal alcohol exposure and FASD. They are novel products that have been evaluated and sustained into routine organisational practice. We also demonstrated that consumer and community participation made a difference to this research and participation was valued by community and consumer representatives and researchers. Project management was comprehensively endorsed by researchers and contributed substantially to the research and benefited both management and scientific outcomes. There are very few previously published reports on consumer and community participation and project management in health and medical research. Our research has made a unique contribution to knowledge and the evidence base about the role of educational resources in the primary prevention of prenatal alcohol exposure and FASD, and to good practice in health and medical research in the areas of consumer and community participation and project management.

Funders of the project: Health Promotion Foundation of Western Australia, Healthway Project Grant #15177; NHMRC Program Grant #353514 (JP, HD'A, CO'L); NHMRC Enabling Grant #402784 (EE); NHMRC Fellowships #353628 (CB) and #457084 (EE).

DEVELOPMENT OF A DIAGNOSTIC INSTRUMENT FOR FETAL ALCOHOL SPECTRUM DISORDERS IN AUSTRALIA (FASD PROJECT)

Winthrop Research Professor Carol Bower & Professor Elizabeth Elliott AM (lead investigators), Dr Rochelle Watkins & Heather Jones (project staff) and the Steering Group: Dr Lucinda Burns, Maureen Carter, Heather D'Antoine, Dr James Fitzpatrick, Associate Professor Jane Halliday, Lorian Hayes, Associate Professor Jane Latimer, Anne McKenzie, Sue Miers AM, Dr Raewyn Mutch, Dr Colleen O'Leary, Jan Payne, Dr Elizabeth Peadon, Elizabeth Russell, Dr Amanda Wilkins.

A modified Delphi process was used to assess expert consensus on the diagnosis of FASD in Australia. A panel of 139 health professionals from Australia (92.2%) and overseas (7.8%) were recruited based on their expertise or involvement in FASD screening or diagnosis. The response rates for rounds 1 and 2 of the survey were 74.1% and 85.4% respectively. Of these health professionals 74.8% were female and 25.2% male with the majority (43.7%) being paediatricians. Only 25.7% of health professionals had completed any specific training on FASD diagnosis. Community conversations were held in Perth and Cairns with 32 women who expected their health professional to provide information on alcohol use in pregnancy. The women also saw merit in having a standard set of questions for all pregnant women that included a question about alcohol use in pregnancy. A final report was submitted to the funding body, the Department of Health and Ageing (DoHA) in September 2011. Papers based on the research are being prepared for publication.

Funders of the project: Department of Health and Ageing; NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB)

EVALUATION OF INFORMATION AND SERVICES FOR PARENTS/CARERS OF CHILDREN WITH A FETAL ALCOHOL SPECTRUM DISORDER

Dr Amanda Wilkins (lead investigator), Winthrop Research Professor Carol Bower and Heather Jones

Focus Groups have been held in Perth and Bunbury to explore events that prompted

parents/foster carers to consider FASD, what initial advice they received, what screening and diagnostic services they were advised to utilise, what the nature of diagnostic services has been, what therapeutic services have been used, what information and services have they found on their own initiative and finally what are the key elements for new resources and support services. A further two focus groups are planned with Aboriginal foster carers in the Perth metropolitan area. A survey will also be conducted with staff within key government and non-government foster care and support agencies on what resources and information they have available to provide to foster carers and for their own professional development. A Reference Group with representatives from the South West Foster Families, Foster Care Association of WA, Wanslea, NOFASARD and Child and Adolescent Community Health Aboriginal Health Team is aligned with the Telethon Institute's policy that consumers and researchers collaborate and draw on each other's knowledge to build on and strengthen the quality of health and medical research. The outcomes from the focus groups will be analysed and reported back to the focus group participants prior to a final report being submitted to the funding body the Foundation for Alcohol Research and Education (FARE) in June 2012.

Funder of the project: Foundation for Alcohol Research and Education (FARE)

KNOWLEDGE, ATTITUDES AND PRACTICE OF FASD WITHIN THE WESTERN AUSTRALIAN CRIMINAL JUSTICE SYSTEM

Dr Raewyn Mutch (lead investigator), Winthrop Research Professor Carol Bower and Heather Jones

In response to comments from lawyers about the inevitability of some children ending up in the criminal justice system Retired District Court Chief Judge, Justice Antoinette Kennedy stated "If we know it's inevitable, why aren't we doing more about it." In 2011 research commenced looking at the 'Knowledge, attitudes and practice of FASD within the WA criminal justice system'. This project aims to find out what people within the justice sector know about FASD, their attitudes towards children and adolescents who may have a disorder in the spectrum and their current practices in dealing with FASD. A Reference Group comprising representatives from WA Police, Law Society of Western Australia, Legal Aid, Department of Corrective Services, Children's Court Judge, National Organisation for Fetal Alcohol Syndrome and Related Disorders (NOFASARD) and the Foster Care Association of WA is guiding the project and assisting with the development of questions for the survey of staff within the justice sector. The survey will have two components: a general section for all participants on demographics and knowledge of FASD and a sector specific set of questions for police, judges and magistrates, corrective services staff and lawyers. The project also aims to identify training and information needs relating to FASD across the justice sector so people with a FASD receive appropriate consideration and referral for services.

Funder of the project: Foundation for Alcohol Research and Education (FARE)

PHARMACOVIGILANCE IN PREGNANCY USING POPULATION-BASED LINKED DATASETS

Lyn Colvin, Linda Slack-Smith, Fiona Stanley, Carol Bower

Recent studies have reported links between prenatal exposure to the group of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) and increased risk of adverse pregnancy outcomes. Using data linkage of population-based health datasets from Western Australia and a national pharmaceutical claims dataset, we investigated the morbidity and mortality outcomes in children born to mothers who were dispensed an SSRI in pregnancy (3,703 women; 3,764 children).

Mean birth weight, length, and APGAR score at 5 minutes were significantly lower in children of women dispensed an SSRI, regardless of whether the SSRI was dispensed in trimester 1, or, trimester 2 or 3 only. 0.9% of the live born children exposed to SSRIs had died before the age of 1 year compared with 0.5% of the unexposed children (odds ratio (OR) 1.8; 95% CI 1.3-2.6). Before the age of two years, 42.9% of the exposed children had been admitted to hospital after their birth admission, compared with 34.1% of the unexposed children (1.4; 1.3-1.6). This may reflect their prenatal exposure to SSRIs, be related to maternal depression, or SSRI use may be a proxy for an environmental exposure such as smoking, or a combination of these factors.

Funders of the project: Australian Postgraduate Award (LC). NHMRC Program Grant #572742; NHMRC Fellowship #634341 (CB)

HARMFUL MATERNAL ALCOHOL CONSUMPTION AND CEREBRAL PALSY IN THE OFFSPRING

O'Leary CM, Watson L, D'Antoine H, Stanley F, Bower C

Heavy alcohol use by pregnant women places the baby at risk of a range of poor outcomes classified as Fetal Alcohol Spectrum Disorders. Cerebral palsy has for many years been thought to be one of these outcomes but the evidence to support this assumption was weak. As cerebral palsy is very rare, research examining this association is difficult to undertake and previous studies had small numbers of children with cerebral palsy. We used routinely collected health data to identify the children of mothers with an alcohol-related diagnosis, a proxy for heavy alcohol consumption, and a randomly selected group of children of mothers without an alcohol-related diagnosis. The birth data for the children were then linked with data from the Cerebral Palsy Register to examine the risk of cerebral palsy in these two groups of children. There were 23,880 children of mothers with an alcohol-related diagnosis and 293 children with cerebral palsy in our study.

We found a three-fold increased risk of pre/perinatally acquired cerebral palsy in children of mothers with an alcohol-use disorder. We also found an eight-fold increased risk of post-neonatally acquired cerebral palsy for non-

Aboriginal children of mothers with an alcohol diagnosis, but not for Aboriginal children. This study provides the strongest evidence that harmful maternal alcohol consumption is a potentially modifiable risk factor for both pre/perinatally and post-neonatally acquired cerebral palsy.

Funders of the project: This study was supported by an Australian National Health and Medical Research Council (NHMRC) Public Health (Australia) Fellowship (594451) (Dr. O'Leary), NHMRC program grant number 353514 (2005-09), and an NHMRC Research Fellowship (353628) (Dr Bower). Dr. O'Leary was partially funded by infrastructure grants from Curtin University and the Western Australian Drug and Alcohol Office.

Intellectual Disability

IDEA - INTELLECTUAL DISABILITY EXPLORING ANSWERS

Carol Bower, Helen Leonard, Ami Bebbington, Amanda Langridge, Patrick Fitzgerald, Geoff Hammond, Jenny Bourke.

The IDEA Database provides an infrastructure for population-based epidemiological research into the causes and prevention of intellectual disability as well as the outcomes for those affected. Information in the database is sourced from data from the Disability Services Commission (DSC) since 1953, as well as information from the Department of Education for births since 1983. IDEA is currently updated with notifications of children identified with an intellectual disability from the Department of Education and the Disability Services Commission to the end of 2008. These records are linked by the Western Australian Data Linkage Unit (DLU) to each other and to all current notifications on the database in order to minimise any duplications. Medical information on cause of intellectual disability is provided from Disability Services Commission.

Analysis of prevalence rates for intellectual disability calculated on the WA births from 1983-2003 and ascertained up to 2008 gives a rate of 17.6/1000 live births. This is an increase on the previous prevalence rate of 14.3/1000 live births, calculated using births from 1983-1992 and ascertained up to 1999. Whilst more recent data are not yet available, further analysis undertaken suggests that the prevalence of mild-moderate intellectual disability may have increased among children born in the nineties. This will be further investigated to try to identify the reason for this rise and whether it might relate to an increase in the diagnosis of autism spectrum disorders or another cause.

Recent articles published in the scientific literature using data from the IDEA database have covered the areas of autism, child maltreatment, evaluation of family-centred care for children with intellectual disability, hospital admissions of children and adolescents with single gene and chromosomal disorders and variation over time in health conditions of children with Down syndrome. Investigations currently underway include the relationship between heavy alcohol consumption during pregnancy and intellectual disability in the offspring; pregnancy and birth factors associated with intellectual disability and autism; hospitalizations in children with intellectual disability and autism: and the pattern of hospitalizations for children with Down syndrome.

The IDEA Database is overseen by the IDEA Advisory Council. The current members are Professor Carol Bower (Chair), Dr Helen Leonard, Jenny Bourke, (TICHR), Dr Vera Morgan (UWA), Richard Sanders (Department of Education), Robyn Cooksey (Department of Education), Kerry Stopher (DSC), Nick Cantatore (DSC), Dr Peter Chauvel (Paediatrician), Dr Peter Rowe (State Child Development Centre) and Charlie Rook (Consumer).

Funders of the project: Disability Services Commission

MULTI-REGISTRY ANALYSES OF PRE- AND PERINATAL RISK FACTORS FOR AUTISM

Michaeline Bresnahan, Kim Carter, Richard Francis, Mika Gissler, Raz Gross, Nina Gunnes, Geoffrey Hammond, Mady Hornig, Christina M Hultman, Amanda Langridge, Helen Leonard, Anastasia Iliadou Nyman, Erik Parner, Manuel Posada, Abraham Reichenberg, Diana Schendel, Sven Sandin, Andre Sourander, Camilla Stoltenberg, Pål Surén and Ezra Susser.

Population-based disease registry systems are extremely important research resources especially for conditions such as autism which are of comparatively low prevalence. Despite numerous studies investigating the association between pre- and perinatal factors and autism, many relationships remain unclear, often because sample sizes are small and methodologies vary across research groups and countries. To overcome these limitations, the International Collaboration for Autism Registry Epidemiology (iCARE) was established among researchers from Denmark, Sweden, Finland, Norway, Western Australia, Israel and the US. The aim of this initiative is to demonstrate the capabilities of a multi-national registry approach to investigate pre- and perinatal factors and autism, autism trends and variation across countries. As all sites have access to complete birth population data for their respective countries/states from which the cases of autism are ascertained, data from the multi-national registries have been used to create a common, harmonised set of variables across all sites. Using a computational infrastructure designed by the bioinformatics team at the Institute, the data, which is stored and managed at each international site, is retrieved on demand and pooled to create a virtual dataset. Analysing this dataset allows us to use the power of data from all countries/states to investigate the relationships between pre and perinatal factors and autism. This virtual dataset also allows cross-country comparisons, and ensures that common methodologies are used. There are several papers currently being prepared for publication.

Funders of the project: Autism Speaks

THE NATURAL HISTORY OF THE CDKL5 DISORDER: DEVELOPMENT OF AN INTERNATIONAL REGISTER

Helen Leonard, John Christodoulou, Meredith Wilson, Alison Anderson, Ami Bebbington, Stephanie Fehr and Jenny Downs

The CDKL5 disorder, which is caused by mutations in the cyclin-dependent kinase-like 5 (*CDKL5*) gene, is a newly identified cause of early-onset seizures and gross motor and intellectual impairment. In the past some children and adults with mutations in the *CDKL5* gene may have been diagnosed with atypical Rett syndrome or infantile spasms.

In 2011, however, we studied questionnaire and genetic data from 86 families living in 14 different countries (majority being USA and UK) who were participating in our InterRett Database. We found that only a minority of children and adults with the CDKL5 disorder did meet the clinical criteria for Rett syndrome. We therefore suggest that the CDKL5 disorder is an independent clinical entity. We also collected photographs of the face, hands and feet of the children in 67 families to investigate whether these children have any characteristic facial features. This work was carried out in collaboration with Professor John Christodoulou and clinical geneticist/dysmorphologist Dr Meredith Wilson, both from the Children's Hospital at Westmead, Sydney. Examination of the photographs confirmed that these children shared similar features of the face and hands. In 2011 we also began collaboration with the International Foundation for CDKL5 Research to establish a new international CDKL5 disorder register using our InterRett database and study processes as a model. This register aims to collect information from additional cases with the CDKL5 disorder from families and their clinicians to increase the precision of our description and will be used to describe the natural history of the disorder. As part of this study, a consumer reference group has been established comprising mothers of a child with the CDKL5 disorder from the USA, UK, Australia and the Netherlands.

Funders of the project: International Rett Syndrome Foundation

THE TRANSITION FROM SECONDARY SCHOOL TO ADULTHOOD: EXPERIENCES AND LIFE OUTCOMES FOR YOUTH WITH AN INTELLECTUAL DISABILITY AND THEIR FAMILIES

Helen Leonard, Carol Bower, Nick de Klerk, Gwynnyth Llewellyn, Stewart Einfeld, Trevor Parmenter, Vivienne Riches, Bruce Tonge, Nick Lennox, Ron Chalmers, John Brigg, Greg Lewis, Jackie Softly, Jenny Bourke, Paula Dyke, Marie-Louise Collins, Sarah Tocker, Kitty Foley, Katherine Bathgate, Terri Pikora, Sonya Girdler

This project, which developed from an ARACY Seed-funding grant, seeks to explore the challenges faced and outcomes achieved by young people with an intellectual disability as they move from secondary school into adult life. There are likely to be major life changes for these young people as they move into adulthood with respect to work, where they live, who cares for them, how their health and therapy needs are managed and how they spend their days. The study is investigating the factors at an individual, educational, family, and societal level which contribute positively and negatively to a 'good' outcome for the young person and their family.

This study involves young people with intellectual disability aged 16 years and over from four separate sources: (i) Down syndrome NOW cohort in WA, (ii) the Queensland Centre for Intellectual and Developmental Disability's ASK study (a five year project aiming to improve the health of young people with intellectual disability by implementing and evaluating the effectiveness of a combined education and health intervention package); (iii) the Australian Child to Adult Development Study at the University of Sydney and (iv) the Australia-wide Rett syndrome cohort. We used the World Health Organization's *International Classification of Functioning, Disability and Health* (ICF) framework which enables us to take into account the complexity of life and acknowledges that many issues come into play which may affect a person's participation in all aspects of life. Environmental factors, which will include family characteristics such as income, availability of transport, parental health and family functioning, as well as the health of the young person and their individual level of functioning, may all contribute to the young person's participation in society.

In 2009/10 questionnaires were administered to 269 families of young people with Down syndrome in Western Australia. Of the 203 (75.0%) returned, 164 (80.8%) had left school with ages varying from pre-transition (16-17 years), early transition (18-20 years) to late transition (23-31 years). Two years later in September 2011, follow-up questionnaires were administered to 228 families and the subsequent response to date has been pleasing. About the same time, questionnaires were sent out to 147 families and care workers of young women with Rett syndrome aged 16 years and over throughout Australia, who are also participating in the transition study.

In consultation with the WA research team and based on our model of collection and storage of data, the Queensland group developed a questionnaire which they administered to the parents of the young people, aged between 17 and 23 years, in the ASK cohort. The response to date is 65% with 54% of these being male. Using the existing ACAD data previously collected in New South Wales and Victoria we hope to compare the effects of legislative and policy differences on employment options between states.

Preliminary findings from our study suggest that the employment needs of about one third of the young people with Down syndrome are not being met, suggesting that services and interventions may not be adequate or appropriate for enabling young adults with Down syndrome to enter the work force. Based on the 2009 Down Syndrome NOW data, among those who had left school (n=164) the most common main day occupation was sheltered employment (39.0%), followed by open employment (25.6%) and alternatives to employment (ATE) (25.0%) while the remainder (10.4%) attended training. We have found that functioning was related to the type of post-school occupation among those who had left

school. Not unexpectedly young adults who were reported as functioning better within self-care, community and communication skills were more likely to be participating in open employment or training than those in sheltered employment or alternatives to employment. However we did not find any evidence that poor health status adversely impacted on workplace participation.

Further analysis will explore additional issues related to employment outcomes to explain why some young people find suitable employment while others do not. These data will also be explored to identify issues related to accommodation and respite needs among this group as well as exploring the longitudinal aspects of parental emotional and physical health.

A lay summary booklet of the findings of previous Down syndrome research undertaken within the group has been published and distributed to all families who have participated in current and previous Down syndrome studies. This publication has also been widely distributed among a range of disability service providers as well as special and local libraries. A copy of the report is available on the website at www.childhealthresearch.org.au.

TOWARDS EVIDENCE BASED CARE FOR RETT SYNDROME: A RESEARCH MODEL TO INFORM MANAGEMENT OF RARE DISORDERS

Helen Leonard, John Christodoulou, Carolyn Ellaway, Lakshmi Nagarajan, Helen Woodhead, Jenny Downs, Elizabeth Geelhoed, Elizabeth Elliott, Peter Jacoby, Ian Torode, Gordon Baikie, Mark Davis, Ian McPhee, Madhur Ravikumara, Sue Thompson, Margaret Thomson Carol Philippe, Ami Bebbington, Amanda Jefferson, Olivia Knight, Sonya Girdler, Anna Urbanowicz, Kingsley Wong, Katherine Bathgate

Rett syndrome is a rare neurological disorder generally 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.

In 2011, a new three year NHMRC funded study commenced to facilitate best practice in clinical decision making, laboratory procedures and counselling in relation to the diagnosis and management of Rett syndrome. This study aims to:

- develop recommendations for the diagnosis process for Rett syndrome;
- identify longitudinal changes in gross motor abilities, hand function and development of scoliosis and;
- evaluate the clinical effectiveness of scoliosis and gastrostomy surgery in children and adults with Rett syndrome.

For the diagnostic study questionnaires relating to the characteristics of their patients are currently being completed by clinicians who request *MECP2* testing from one of the three Australian accredited laboratories. These are completed prior to the result of genetic testing being known. The goal is to develop tools to support clinical decision making to facilitate timely diagnostic testing for girls with Rett syndrome, thereby assisting families in the often stressful early stage when seeking a diagnosis.

As part of the longitudinal study follow-up questionnaires were administered in September 2011 to 269 families enrolled in the study. The response fraction from parents and care-workers has been excellent at over 70% and we anticipate further returns in 2012. Information is being 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 started to be collected and will continue throughout 2012. 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 there is a need to provide accurate information to both clinicians and families of 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 follow-up questionnaire and hospital records has commenced to address these gaps in knowledge and will continue throughout 2012. We will also collect additional video data throughout 2012.

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. This year one focus of the meetings has been the planning of a national family conference to be held in Brisbane in May 2012, to coincide with the International Child Neurology Conference. In November 2011 the new AussieRett website went live and included information about Rett syndrome and the AussieRett study, links to published research abstracts, information about media and current events and links to the online follow-up questionnaire. Importantly, lay summaries of publications or 'research snapshots' are available.

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, Sydney, the Royal Children's Hospital, Melbourne, the Mater Children's Hospital, Brisbane and the Royal Children's Hospital, Brisbane.

During 2011 eleven articles relating to the study were published or accepted for publication. These articles investigated gross motor and hand function over time with video data; the attainment of early developmental milestones and their relationships with regression and diagnosis; health and related services use and costs; physical activity measured by accelerometry, and trends in diagnosis over time. One article was written by an Australian mother together with researchers on her experiences of diagnosis and this paper was published as a companion piece to an article looking at pathways to diagnosis by families with a daughter with Rett syndrome in China recruited through the InterRett database.

Funders of the project: Current: NHMRC Project Grant (1004384), NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568)

INTERNATIONAL RETT SYNDROME STUDY: INTERRETT

Helen Leonard, Alison Anderson, Ami Bebbington, Sally McIlroy, Nada Murphy, Stephanie Fehr, Jenny Downs, Heidi Meyer, Joanne Lee

The InterRett project is now in its 10th year and continues to be an exemplary model for rare disease research. This 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 resulting data repository, which now contains 2,496 cases, affords investigation of a wide variety of issues and our current analysis is concerned with epilepsy.

In addition to the analysis of questionnaire data, we have over the course of 2011 collected qualitative data about the period of regression in interviews with mothers of girls with Rett syndrome. The interviews are providing a developmental profile prior to and over the course of the regression period. Regression is a core feature of Rett syndrome but as yet, has not been the topic of focussed research. Research publications over the last few years have included: the characteristics that influence diagnosis; pain sensitivity; the influence of DNA variations in the *BDNF* gene on severity; and comparisons of clinical outcomes between those with different types of mutations in the Rett syndrome gene *MECP2*. Strong collaboration with colleagues in China continues to be fruitful with a recent publication on the parental origin and recurrence risk in Rett syndrome and an article about barriers to diagnosis of a rare neurological disorder in China. The InterRett project website was recently updated and includes lay term snapshots of these and other research outcomes. Members of the Rett syndrome team, who manage the InterRett project, continue to work with the international research community to harmonise data collection initiatives across countries.

Promotion of the InterRett project is ongoing and encourages clinician and family participation in accordance with the website motto: "Every individual contribution adds to our collective understanding of Rett Syndrome."

Funders of the project: International Rett Syndrome Foundation

DEVELOPING CLINICAL GUIDELINES FOR THE MANAGEMENT OF GASTRO-INTESTINAL DISORDERS AND BONE HEALTH IN PATIENTS WITH RETT SYNDROME

Jenny Downs, Helen Leonard, Gordon Baikie, Madhur Ravikumara, Nusrat Naseem, Amanda Jefferson, Helen Woodhead, Sue Fyfe, Aris Siafarikas

Rett syndrome is often associated with poor growth, in part from feeding difficulties and/or gastro-oesophageal reflux. Co-morbidities such as constipation and abdominal bloating are also common. There is limited literature of management strategies for these common gastro-intestinal disorders in Rett syndrome and we have used the Delphi technique to develop a consensus for items that describe how to assess and manage these gastro-intestinal disorders. We recruited an expert panel of clinicians and researchers who reviewed two drafts of the guidelines. We have know identified the consensus for each of the items and are currently preparing three manuscripts for publication.

Rett syndrome is also associated with osteoporosis and a greater likelihood of fracture in comparison with the general population. We are also developing a set of guidelines for optimal bone health in Rett syndrome. Our methods have thus far included assessment of the perspectives of parents on these issues, systematic review of the literature and the creation of a document for circulation in the first phase of the Delphi process. We are now recruiting an expert panel which is both international and muli-disciplinary in nature who will participate in the Delphi process and provide feedback on the first and subsequent drafts until a consensus is reached.

Funders of the project: Rett Syndrome Association UK.

WA REGISTER FOR AUTISM SPECTRUM DISORDERS

Emma Glasson, Katherine Russell-Smith, Ainsley Read, Carol Bower.

The aim of the WA Register for Autism Spectrum Disorders is to monitor diagnostic trends of conditions characterized by autism (autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)). These disorders develop in young children and have significant life-long effects in the areas of social interaction, communication and behaviour. The WA Autism Register is ongoing and between 1999 and 2011 information has been collected on more than 4,000 individuals.

As well as existing for the purpose of local and national information, Register data were used in an international collaboration making comparisons with a Danish autism register. This

project was awarded funding from Autism Speaks (USA, value $128,000) and findings were published during 2011:

Parner E, Thorsen P, Dixon G, de Klerk N, Leonard H, Nassar N, Bourke J, Bower C & Glasson E (2011). A comparison of autism prevalence trends in Denmark and Western Australia. *Journal of Autism and Developmental Disorders*, 41(12):1601-1608.

Funders of the project: Autism Speaks

WESTERN AUSTRALIAN AUTISM BIOLOGICAL REGISTRY

Andrew Whitehouse, John Wray, David Ravine, Anna Hunt, Rachel Jones

The aim of the Western Australian Autism Biological Registry (WAABR) is to collect detailed information on children with autism in WA and their families and to centralize this information so that it is accessible to those who are involved in autism research. The study has three components to allow us to obtain the best information about the child with autism. These are questionnaires, clinical assessment and blood samples of the child and parents. The WA Autism Biological Registry began its recruitment in early 2011, with our first participant coming through the doors in March 2011. In late 2011, we had seen our 100th participant. To date, we have seen 150 participants with another 50 booked in to be seen over the next few months. This makes WAABR the largest biobank of autism information in the southern hemisphere. Our aim is to reach 500 families within the next two years.

Funders of the project: National Health & Medical Research Council

THE FLUOXETINE FOR AUTISTIC BEHAVIOURS TRIAL

Andrew Whitehouse, John Wray, Jo Granich, Dinah Reddihough, Catherine Marraffa, Philip Hazell, David Dossetor

Repetitive behaviours (RBs) constitute one of the three core impairments that affect children and adolescents with an autism spectrum disorder (ASD). These behaviours are typically initiated and exacerbated by associated anxieties that can significantly impact upon daily life. The Fluoxetine for Autistic Behaviours (The FAB Trial) is a multi-site randomized controlled trial seeking to investigate the use of Fluoxetine (anti-depressant medication also known as Prozac) for the treatment of RBs for the first time in Australia. Lack of gold standard evidence for the effectiveness, optimal dosing and safety of Fluoxetine has meant that this medication is commonly used "off the label" as treatment for RBs and anxieties among the paediatric population living with ASD. The recruitment for eligible participants (aged 8-17 years) across all sites (WA, NSW and Victoria) has been wide-spread and continuing with over 40 children participating in this trial to date.

The findings of this trial will provide evidence-based information for individuals with ASD and their families. The research outcomes will enable families to make better informed decisions about placing their child on this medication as a way of managing their symptoms of ASD. Similarly, the results will inform physicians and provide sound clinical guidelines and practice related to the use of Fluoxetine and its appropriateness for RBs including the plausible side-effects of this medication for this population. The FAB trial is expected to finish in 2013.

Funders of the project: National Health and Medical Research Council

PREGNANCY INVESTIGATION OF SIBLINGS AND MOTHERS OF CHILDREN WITH AUTISM (PRISM)

Andrew Whitehouse, Murray Maybery, Cheryl Dissanayake, Martha Hickey, Craig Pennell, Jo Granich, Anna Hunt, Lisa Unwin

Studying fetuses 'at risk' for autism is the aim of a world-first longitudinal research study named PRegnancy Investigation of Siblings and Mothers of children with autism (PRISM). This NHMRC funded study is seeking to investigate specific *in utero* bio-markers for autism by looking at aspects of fetal development, such as fetal brain growth and the prenatal hormone environment. State-of-the-art ultrasound technology used at six gestational time points (12, 18, 24, 28, 32 and 36 weeks) is enabling this aspect of pregnancy to be examined among two groups of women. Pregnant mothers with subsequent pregnancies who have an existing child with autism (cases) are compared with mothers who have a child with neuro-typical development (controls). Newborns umbilical cord blood is collected to further study the DNA and examine their exposure to pregnancy hormones. Children's growth and development is monitored via standard measures and direct observations at four time points until their second birthday.

Over 30 women are now participating in this research across both arms of the study. By the end of 2015, we aim to recruit over 200 pregnant mothers. The findings of this research may provide insight into the early onset and atypical development of fetal brain growth. In addition, the study outcomes may lead to a breakthrough in identifying specific biological risk factors for autism early in life. This may have implications for the development of preventative in-utero measures. Collectively, the results of this study will bear significant implications on early diagnosis of autism and possible commencement of early intervention therapies for the treatment of autism among much younger children than ever before. Overall, the PRISM findings are likely to have enormous impact on the future outcomes of young children affected by autism and their families.

Funders of the project: National Health and Medical Research Council

WA CEREBRAL PALSY STUDIES

Eve Blair, Linda Watson, Fiona Stanley

Cerebral palsy (CP) is a chronic neurological condition affecting movement and posture,

ranging in severity from barely noticeable to severely disabling. For most, the cause is unknown. CP results in life-long disability, and as there is no cure, prevention and effective management are top priorities.

THE WESTERN AUSTRALIAN CEREBRAL PALSY REGISTER

Linda Watson, Eve Blair, Fiona Stanley

The WA CP Register, now in existence more than 30 years, is used to monitor the occurrence of CP in WA, carry out research to investigate its causes and evaluate treatment strategies, identify CP as a long-term outcome in other WA studies and assist in the planning of services for people with CP. A birth cohort is included in analyses after case data are updated at age 5 years; the Register is now considered complete to 2006.

The WA Register is now also responsible for contributing data to the Australian CP Register (ACPR), a national collaboration initiated by the WA team which was established to provide information about CP throughout Australia as well as a larger study population to enable more effective research. The administrative centre has now moved to the Cerebral Palsy Institute in NSW where it continues to flourish. The first report of the ACPR was published at the very end of 2009, Eve Blair presented the results of this report both at the AusACPDM meeting in Christchurch, New Zealand and at the AACPDM meeting in Washington, USA.

Funders of the project: The WA Cerebral Palsy Register is presently funded by NHMRC Program Grant #572742 Early developmental pathways linking health, disability, education, welfare and justice (2010-2014)

DEVELOPING A RELIABLE SYSTEM OF CLASSIFYING CP

Sarah Love, Noula Gibson, Eve Blair, Linda Watson

The cerebral palsies include a wide range of motor impairments across the spectrum of severities, and research therefore depends on consistency in classifying CP subgroups. International attention has been focused on the challenge of standardising the recording of motor impairments for several decades, and WA has long been at the forefront in developing a reliable system of describing the clinical features of CP. We are continuing to introduce and trial an innovative diagrammatic limb-by-limb CP Description Form which incorporates the Australian Spasticity Assessment Scale (ASAS) devised by Sarah Love and Noula Gibson, who have led this work. A booklet which defines every aspect of the form is currently being compiled. A Training and Reference video demonstrating the use of the ASAS as well as the features of different forms of CP is close to completion.

Funders of the project: PLAN Australia has generously funded the development of the ASAS, the CP Description Form and the Training and Reference DVD. A PMH Foundation Special Project Grant 2007 covers travel to conduct training sessions throughout WA, and an Innovative Research Grant from the CP Institute funds the extension of training across Australia

CASE CONTROL STUDIES OF CP IN TERM AND PRE-TERM INFANTS IN WA, 1980 TO 1995

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

Comprehensive maternal, birth and neonatal information on CP cases, matched controls, and a sample of unexplained perinatal deaths born 1980-1995 was collected from birth hospitals throughout the State providing a wealth of data enabling causal pathways to the different outcomes to be compared. The primary aim of these studies is to prevent the occurrence of brain damage responsible for CP by identifying points on each causal pathway to CP at which it may most effectively, efficiently and ethically be interrupted. Data analysis continues with the intent to explore causal pathways and report research findings at international forums.

Funders of the project:

This case-control study has been s funded by NHMRC Program Grants #353514 (2005-2009) and #572742 (2010-2014). An Innovative Research Grant from the CP Institute provides additional funds for analysis and travel

Childhood Cancer

AUSTRALIAN STUDY OF CAUSES OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN

Elizabeth Milne, Carol Bower, Nick de Klerk, Ursula Kees, in collaboration with Bruce Armstrong, Frank van Bockxmeer, Michelle Haber, Rodney Scott, John Attia, Murray Norris, Lin Fritschi, Margaret Miller, Judith Thompson, Frank Alvaro, Catherine Cole, Luciano Dalla Pozza, John Daubenton, Peter Downie, Marie Kirby, Liane Lockwood, Glenn Marshall, Elizabeth Smibert, Ram Suppiah

Researchers in the Childhood Cancer Epidemiology program have been analysing the data collected between 2003 and 2007 in this national case-control study of the causes of childhood acute lymphoblastic leukaemia (ALL). The primary hypothesis of this study was that maternal folate supplementation during pregnancy protects against ALL in the offspring, with the effect modified by genetic factors in folate metabolism.

The following papers were published in 2011:

Parental prenatal smoking and risk of childhood ALL

In this paper we reported that maternal smoking during pregnancy was not related to risk of ALL but that paternal smoking of 15 or more cigarettes per day in the preconception period was moderately related to risk of ALL. When our results for paternal smoking were combined with others from around the world there was evidence that smoking 20 or more cigarettes a day increased the risk of childhood ALL.

Exposure to house painting and the use of floor treatments and the risk of childhood acute lymphoblastic leukemia

In this paper we reported some suggestion of an association between house painting and an increased risk of ALL if more than three rooms in the house had been painted, if someone

other than the parents had done the painting (possibly due to type or quantity of paint used by professionals), or if the mother had painted with oil-based paints outside the house.

Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukemia

In this paper we reported modest evidence that the use of professional pest control treatments during pregnancy and shortly after the child's birth may increase the risk of ALL. The risk was highest for exposure after birth between the ages of two and three years, and was also higher if the house had been treated for termites. When results from other studies around the world were combined with the current results, there was an increased risk of pest control treatments during pregnancy.

Refueling of vehicles, the use of wood burners and the risk of childhood acute lymphoblastic leukemia

In this paper we reported no association with the refueling of vehicles by the mother before or during the pregnancy or the father in the year before the pregnancy and risk of ALL. There was a moderate association between using a closed wood burner in the year before or during pregnancy, which was slightly less for after birth. There was no increasing risk with greater usage of wood burners, which might indicate that these results are due to chance.

Risk of childhood acute lymphoblastic leukaemia following parental occupational exposure to extremely low frequency electromagnetic fields

In this paper we reported that we saw no evidence of an association between maternal or paternal antenatal exposure to ELF and risk of childhood leukaemia.

Parental occupational exposure to exhausts, solvents, glues and paints and risk of childhood leukaemia

In this paper we reported that antenatal exposure to moderate or substantial levels of exhausts by mothers or fathers increased the risk of leukaemia in their offspring.

Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: Results from an Australian case-control study.

In this paper we reported that children of mothers who drink at least two cups of coffee a day during pregnancy and do not smoke may be at increased risk of leukaemia. In addition, the risk of specific types of leukaemia involving chromosomal translocation was higher among children of mothers who drank at least two cups of coffee or tea per day during pregnancy.

Analysis is also under way to examine whether there are links between risk of ALL and:

- the mothers' diet during pregnancy;
- the types of jobs that parents had
- parental alcohol consumption
- variations in genes that influence the way the body processes food and chemicals
- medication use before/during pregnancy and by the child

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

NATIONAL CASE-CONTROL STUDY OF THE CAUSES OF CHILDHOOD BRAIN TUMOURS

Elizabeth Milne, Carol Bower, Nick de Klerk, Peter Dallas, in collaboration with Bruce Armstrong, Frank van Bockxmeer, Rodney Scott, John Attia, Lin Fritschi, David Ashley, Lesley Ashton, Judith Thompson, Murray Norris , Richard Cohn, Margaret Miller, Luce dalla Pozza, John Daubenton, Timothy Hassall, Maria Kirby, Stewart Kellie, Ross Pinkerton, Frank Alvaro, Angela Alessandri

The Australian Study of Childhood Brain Tumours (AUS-CBT) was a national case-control study into the causes of childhood brain tumours (CBT). It aimed to investigate genetic, dietary and environmental risk factors for CBT, and is the sister study to the Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (AUS-ALL). The study recruited case and control families between 2006 and 2010; data collection was completed in 2011.

The study involved children aged 0-14 years. Case children and their parents were recruited from the nine paediatric oncology units nationwide. In total, we were notified of 734 eligible cases, of whom 568 were invited (77%) to participate and 374 consented, with 335 providing either self-administered questionnaires or doing short telephone interviews to provide demographic and basic exposure data. 302 case families returned full exposure questionnaires, and 295 did a food frequency questionnaire. We received DNA samples from 355 families for genotyping, which is complete. A total of 194 families declined to participate or could not be re-contacted, and a further 162 were not invited due to medical or psychosocial reasons.

Control children (that is, children without a brain tumour) and their families were recruited through national random digit dialling 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 paper was accepted for publication in 2011:

Participation in population-based case–control studies: does the observed decline vary by socio-economic status?

In this paper we compared the socioeconomic status of recruited controls in the Aus-ALL study and the Aus-CBT study. We found that participation rates were lower in Aus-CBT than Aus-ALL, and that controls from both studies had higher socioeconomic status than that of the general population, but were quite similar to each other.

Analysis and manuscript preparation are under way to examine whether there are links between risk of CBT and:

- Maternal folate supplementation
- Parental alcohol consumption prior to or during the pregnancy
- Parental smoking prior to or during pregnancy

- Maternal consumption of coffee and tea during pregnancy

Funders of the project: NHMRC Grant #404089

NUTRITION AND GENOME HEALTH IN CHILDREN

Elizabeth Milne, Michael Fenech, Bruce Armstrong, Nick de Klerk, Margaret Miller

The Nutrition and Genome Health in Children Study aimed to identify key nutritional and genetic factors associated with DNA damage in children. It aimed to describe the nature of the interaction between nutritional and genetic factors in determining level of DNA damage in children, and also the associations between body mass index, DNA damage and micronutrient levels in children.

This study was a cross-sectional study of 450 Western Australian children, conducted between 2009 and 2011. Participants were children aged 3, 6 or 9 years at recruitment who had never been diagnosed with asthma, diabetes, cancer, arthritis or epilepsy. Participants and their parents were recruited via primary schools, posters displays and flyers, advertisements in local newspapers and information letters distributed to a wide range of organisations. 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 dietician where needed.

In all, 464 participants provided data. Statistical analysis of these data is currently in progress.

Funders of the project: NHMRC Grant#572623

Infectious Diseases

AETIOLOGY, BURDEN AND CAUSAL PATHWAYS OF ACUTE LOWER RESPIRATORY INFECTIONS USING POPULATION LINKED DATA

Hannah Moore, Deborah Lehmann, Khadra Jama-Alol, Peter Jacoby, Nicholas de Klerk in collaboration with Peter Richmond, David Smith, Anthony Keil, Christopher Blyth

Acute lower respiratory infections (ALRI), or chest infections like influenza and pneumonia, are a major cause of illness in young children. The primary objective of this project is to describe the aetiology, burden and causal pathways of ALRI in Aboriginal and non-Aboriginal children from a 10-year birth cohort (245, 249 births) using population linked data from the Western Australian Data Linkage System. Datasets include the Midwives' Notification System, Hospital Morbidity Database System, Birth and Death Register, Emergency Department Data Collection, Birth Defects Register and the PathWest Laboratory Database. This project is the first to link statewide laboratory data for respiratory pathogens to other datasets within the Western Australian Data Linkage System. Data analysis was completed in 2011 and results are now being disseminated. Major findings in 2011 were:

- 43,003 laboratory records for respiratory pathogen testing between 2000 and 2005 from children in the birth cohort were identifed. Of these, 89.7% have a coded result for 30 bacterial and viral respiratory pathogens.
- Linking laboratory data and hospital data, we reported that 57.9% of linked hospitalisation records for ALRI had tested positive for a respiratory pathogen. Of these, respiratory syncytial virus was the most common (39.5%) and was identified in 63.7% of bronchiolitis admissions for children under 6 months. Many respiratory pathogens were found across different clinical diagnoses.
- Non-Aboriginal children delivered by elective caesarean have an increased risk of repeated hospitalisations for bronchiolitis compared to those non-Aboriginal children who were delivered through spontaneous vaginal delivery. This finding attracted widespread local and national media.
- Through the analysis of linked emergency department data, we investigated the out-of-hospital burden of ALRI in children from the birth cohort. Bronchiolitis and croup were the most common reasons for presentation. However, there are some limitations of the available emergency department datasets.
- Children born with birth defects have an increased risk of hospitalisation before age 2 years for ALRI than children without birth defects. This increased risk remains after adjusting for other known risk factors for hospitalisation.

The majority of these findings have now been published in international and national peer-reviewed journals. A further manuscript describing metropolitan emergency department presentations for respiratory infections is currently under review and a manuscript describing the relationship between birth defects in children and hospitalisations for ALRI is in advanced draft stage. In 2011, these findings were presented at the Exploiting Existing Data for Health Research International Conference in Scotland, the 7th World Congress of the World Society for Paediatric Infectious Diseases in Melbourne, the Communicable Disease Control Conference in Canberra and the Australasian Epidemiological Association Annual Scientific Meeting in Perth. This project also contributed to the completion of Hannah Moore's PhD which was awarded in July 2011.

Funders of the project: NHMRC Project Grant #572590.

HOSPITALISATION FOR DIARRHOEA AMONG WESTERN AUSTRALIAN CHILDREN

Deborah Lehmann, Hannah Moore

Diarrhoea is a significant reason for hospitalisation in Australian children. This study utilising the total population-based databases from the Maternal and Child Health Research Database investigates the trends in hospital admissions for diarrhoeal diseases (gastroenteritis) in Western Australian children aged <15 years between 1983 and 2006. Hospitalisation rates for gastroenteritis are highest in children aged 6-12 months. Over the last two decades, we have seen diverging trends in hospitalisations for gastroenteritis between Aboriginal and non-Aboriginal children. In Aboriginal children aged 6-11 months, rates have fallen from 304 per 1000 population in 1983-1994 to 214/1000 in 1995-2006 with similar declines in other age groups. In non-Aboriginal children, hospitalisation rates for gastroenteritis have increased from 1987 to 1999 and then declined from 2001 to 2006 when they were approximately 20/1000 in those aged 6-11 months. There have also been diverging trends of gastroenteritis hospitalisations between the different geographical regions of the state. This study will be useful in providing baseline data on hospitalisations for diarrhoeal disease prior to the introduction of the rotavirus vaccine in 2007. A publication describing the temporal and seasonal trends over a two decade period is now in advanced draft form.

Funders of the project: NHMRC Program Grant #353514

MONITORING CARRIAGE OF *STREPTOCOCCUS PNEUMONIAE* AMONG ABORIGINAL CHILDREN AND ADULTS IN WESTERN AUSTRALIA

Deborah Lehmann, Anke Hoskins, Deirdre Collins, in collaboration with Jacinta Bowman, Natalie Thomsen, Jade Jones, Tom Riley, Carolien Giele, Paul Effler, Amanda Leach, Kim Hare, Heidi Smith-Vaughan, Peter Richmond

Streptococcus pneumoniae (pneumococcus) can cause middle ear infections and invasive pneumococcal disease (IPD) resulting in meningitis, pneumonia and septicaemia (blood poisoning). The Australian Aboriginal population has among the highest reported IPD rates worldwide. The existence of over 90 known types (serotypes) of pneumococci increases the challenge of prevention. A pneumococcal conjugate vaccine (Prevenar™, PCV7) covering the 7 most common serotypes causing IPD in a 2-4-6-month schedule and an 18-month booster with a pneumococcal polysaccharide vaccine (Pneumovax™) covering 23 serotypes have been offered to Aboriginal children since 2001. Pneumovax™ is also offered to adults. While there has been a marked reduction in IPD due to the near elimination of Prevenar™ serotypes, there has been an increase in IPD rates due to serotypes not included in the Prevenar™ vaccine, particularly in young Aboriginal adults. In light of this, Prevenar™ was replaced with Prevenar-13™ on 1 July 2011, which covers 6 additional serotypes. The findings of increasing incidence of IPD due to non-PCV7 serotypes in the West Australian Aboriginal population is consistent with national and international data. Our data help to inform policy on optimal vaccine schedules and formulation.

Pneumococci are carried in the back of the nose of healthy as well as sick individuals. Surveillance of pneumococcal carriage offers important complementary information to data on IPD since it can quickly provide a large amount of information on serotypes circulating in the population, thereby informing public health programs. It also gives a conservative estimate of antibiotic resistance of invasive pneumococcal strains. This study aims to monitor pneumococcal carriage by collecting 600 pernasal swabs from Aboriginal adults and children in urban, rural and remote areas of Western Australia annually. We also collect ear swabs from children with middle ear discharge and data on vaccination status of children in the study.

Other study aims include:

i) describing the prevalence of upper respiratory tract (URT) carriage of other pathogens identified on primary culture;

ii) comparing the distribution of pneumococcal serotypes in the URT with those causing IPD in Aboriginal adults and children annually;

iii) storing pernasal swabs for detection of viruses by PCR to describe the prevalence of respiratory viruses; and

iv) investigating viral-bacterial interactions in the URT.

We recruit study participants attending health services for routine examination, immunisation or illness and also through home-visiting or community links. To date we have collected 1578 pernasal swabs and 58 swabs of discharge from the middle ear from a total of 559 children aged < 5 years and 1010 older children and adults. Most of the collected swabs (1518) have been cultured. Recruitment has taken place in Wiluna, Kalgoorlie, Coolgardie, Laverton, Leonora, Mt Margaret, Coonana, Norseman, Roebourne, Wickham, Kununurra, Broome, Beagle Bay, Halls Creek, Carnarvon, Jigalong, Meekatharra, Burringurrah, Bunbury, Geraldton and at Aboriginal Medical Services in the Perth Metropolitan area (Perth, Armadale, Bentley, Maddington, Swan District and Kwinana).

In children under 5 years of age pneumococci were grown from 70% of pernasal swabs. *Haemophilus influenzae* from 62% and *Moraxella catarrhalis* from 68%. In people aged ≥5 years 35% of pernasal swabs grew pneumococci, 22% grew *H. influenzae* and 27% grew *M. catarrhalis*. 42 different serotypes have been identified. Currently, the most common pneumococcal serotypes in children under 5 are 6A, 23F and 19A, while 6C, 16F and 6A are most common in older children and adults.

In line with data from IPD surveillance in WA Prevenar™ successfully eliminated carriage of serotypes included in this vaccine since only 12% of pneumococci were Prevenar™ serotypes. 66% of pneumococci in the URT were serotypes that are not covered by Prevenar-13™. Ongoing surveillance of pneumococcal carriage following the change-

over to Prevenar-13™ is vital for development of appropriate guidelines for Aboriginal people.

Our findings to date were presented at the Communicable Disease Control Conference in Canberra in April 2011, and the 7th World Congress for the World Society for Paediatric Infectious Diseases in November 2011 in Melbourne.

Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation and NHMRC Project Grant #545232 (a collaboration with Menzies School of Health Research)

INVESTIGATING THE RISK FACTORS AND CO-MORBIDITIES ASSOCIATED WITH INVASIVE PNEUMOCOCCAL DISEASE IN THE WESTERN AUSTRALIAN POPULATION

Deborah Lehmann, Aoiffe McLaughlin, Hannah Moore

The Vaccine Impact Surveillance Network (VISN) conducted enhanced surveillance on Invasive Pneumococcal Disease (IPD) between 1996 and 2007. Everyone is susceptible to IPD, though most at risk are children under the age of 2 years, elderly persons and those with chronic disease and compromised immune systems. Across all age groups incidence rates are higher in Aboriginal people than in non-Aboriginal people throughout Australia. The Australian Aboriginal population has among the highest reported IPD rates worldwide. Since January 2008, CDCD has conducted the surveillance of IPD across Western Australia. Our previous publications reported on the incidence and serotype distribution of IPD notifications in the WA Aboriginal and non-Aboriginal population. This project involves analysis of the IPD surveillance data between 1997 and 2007 to investigate the underlying co-morbidities and risk factors associated with IPD. These include an investigation of risk factors such as excessive alcohol use, smoking, diabetes, asthma, chronic diseases of the respiratory system, chronic diseases of the cardiac system and malignancies. This project aims to describe the co-morbidities reported in IPD cases according to age, gender, geographical region and Aboriginal status. We will also investigate the NHMRC recommendation for the 23vPPV vaccine to be given to those individuals aged ≥10 years with certain risk factors for IPD. Analyses for this project are ongoing and a publication from these descriptive analyses is planned.

Funders of the project: Western Australian Department of Health through the Collaboration for Applied Research and Evaluation

THE KALGOORLIE OTITIS MEDIA RESEARCH PROJECT - AN INVESTIGATION INTO THE CAUSAL PATHWAYS TO OTITIS MEDIA IN ABORIGINAL AND NON-ABORIGINAL CHILDREN

Deborah Lehmann, Peter Jacoby, Wenxing Sun, Alicia Annamalay, Christine Jeffries-Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane, Ruth Monck, Fiona Stanley, in collaboration with Bega Garnbirringu Health Services, Ngunytju Tjitji Pirni Inc, Harvey Coates, Thomas Riley, Sharon Weeks, Allan Cripps, Jennelle Kyd, Jacinta Bowman, Amanda Taylor, Gerry Harnett, David Smith, Glenys Chidlow, Denise Murphy, Kylie Carville, Stefano Occipinti, Amanda Leach, Nevada Pingault

Otitis media (OM, middle ear infection) can seriously affect childhood development, school performance and subsequent social and economic well-being. The Kalgoorlie Otitis Media Research Project was established in 1999 to investigate the causal pathways to OM and, specifically, to identify demographic, socio-economic, environmental, microbiological and immunological risk factors for OM in Aboriginal and non-Aboriginal children in order to develop appropriate interventions. We followed 100 Aboriginal and 180 non-Aboriginal children from birth to age two years. Field work was completed in 2004 and data cleaning completed in April 2005. Analysis of data has been on-going.

Major findings:

- The peak prevalence of OM in the Kalgoorlie-Boulder area was 72% in Aboriginal children aged 5-9 months and 40% in non-Aboriginal children aged 10-14 months.
- Almost one-third of Aboriginal children and 5% of non-Aboriginal children had a perforated ear drum at least once by age 2 years.
- 65% of Aboriginal children and 23% of non-Aboriginal children have some degree of hearing loss at age 12-17 months.
- Measurement of otoacoustic emissions in early infancy can identify children at subsequent risk of OM.
- Exposure to environmental tobacco smoke is an important risk factor for OM.
- Crowding is the strongest and most consistent predictor of carriage of OM-associated pathogens *S. pneumoniae*, nontypeable *H. influenzae* or *M. catarrhalis* in the URT, but living in a larger house attenuates this effect in Aboriginal children.
- Daycare attendance predicts carriage of the same OM-associated pathogens in non-Aboriginal children while exclusive breastfeeding for the first 6-8 weeks of life protects children from carriage of *Staphylococcus aureus*.
- Rhinoviruses (HRV) and adenoviruses were commonly identified in asymptomatic children, more commonly in Aboriginal than non-Aboriginal children and are frequently associated with bacterial carriage.
- Human rhinovirus A is the most common virus type identified in healthy children and HRV C is associated with presence of upper respiratory symptoms and carriage of bacteria associated with OM.
- Early carriage of *H. influenzae* increases risk of OM in Aboriginal children, while early carriage of *M. catarrhalis* increased risk of OM in non-Aboriginal children.
- A large proportion of *M. catarrhalis* strains were resistant to ampicillin and/or co-trimoxazole. Therefore, current therapeutic guidelines, which recommend amoxicillin for treatment of OM, may need to be revised. We have also documented for the first time simultaneous carriage of multiple

strains of *M. catarrhalis*.

- Early nasopharyngeal colonisation can modulate mucosal immune responses in the upper airways. Total salivary IgA is stimulated by high bacterial load, but levels of specific antibodies to bacteria associated with OM may be suppressed by early colonisation in Aboriginal children.

Funders of the project: Western Australian Health Promotion Foundation (Healthway); NHMRC Project Grant #212044 and as part of the NHMRC Program Grant #353514

PREVENTING OTITIS MEDIA TO GIVE A SOUND START FOR SCHOOL (PINA PALYA PINA KULILKU, GOOD EARS GOOD LEARNING)

Deborah Lehmann, Ruth Monck, Wendy Sun, Lorraine Sholson, Kirsten Alpers, Margaret Wallam, Daniel McAullay, Tanyana Jackiewicz in collaboration with Anne Mahony, Charles Douglas, Michelle Forrest, Bega Garnbirringu Health services, Ngunytju Tjitji Pirni Inc, Francis Lannigan, Sharon Weeks, Annette Stokes, Christine Jeffries-Stokes

This 3-year project follows on from findings of the Kalgoorlie Otitis Media Research Project. We reported very high rates of otitis media (OM) and associated hearing loss, high carriage of bacteria in the upper respiratory tract (which predisposes to OM) from a very young age in Aboriginal children and an increased risk of OM among children exposed to environmental tobacco smoke. The overall aim is to have Aboriginal children hearing well by the time they start school.

The objectives of this project are to:

(1) Develop and implement a multifaceted ear health promotion program in collaboration with Aboriginal organisations in the Goldfields.

(2) Evaluate the impact and effectiveness of an ear health promotion program that includes (a) an awareness program, (b) training of Community Health Nurses and Aboriginal Health Workers in screening and health promotion and (c) a screening program for OM.

(3) Evaluate use at primary health care level of a simple tool (which measures otoacoustic emissions) that can detect fluid in the middle ear at a very young age and hence identify a target group of children at subsequent risk of developing OM.

(4) Evaluate the overall program in terms of feasibility and sustainability.

During 2011, enrolment continued and ear screenings were conducted in Kalgoorlie, Coolgardie, Norseman, Laverton, Mt Margaret and Leonora. Over 200 Aboriginal children under 5 years of age have been enrolled and 330 ear examinations performed. For examinations where a diagnosis could be made, 51% were found to be normal in both ears and in 49% OM was found in one or both ears with perforations of the eardrum present in 37% of these examinations (19% of the total valid examinations). Early screening enabled many children to be seen by ENT specialist Dr Francis Lannigan at clinics in Kalgoorlie and Leonora.

A variety of activities involving adults and children that promoted handwashing and keeping children away from cigarette smoke were organised. Music workshops conducted by a local Indigenous musician in 3 primary schools and a community centre were warmly received and culminated in performances of stories and 'The Germ Song' by the children. Soap making was offered at community events and at some screening sessions. Training and encouragement of health workers occurred during ear screening sessions and as part of the curriculum at Bega Nindila Training Centre.

The video-otoscope proved to be very useful for helping carers, children and health workers understand and visualise the anatomy of the ear and the need for regular ear checks. An interactive inflatable ear that children and adults can walk through was developed and commissioned with community consultation taking place in November 2011 and a multi-agency community event scheduled for the launch of the 'Big Ear' in early 2012.

Media interest in the study included radio interviews and articles in the Kalgoorlie Miner newspaper on the children's musicals and the development of the Big Ear.

The study was presented at:

The 11th National Rural Health Conference, March 13-16, Perth

Funders of the project: Western Australian Health Promotion Foundation (Healthway)

INFECTIOUS DISEASES COMMUNITY REFERENCE GROUP

Deborah Lehmann, Hannah Moore, Kirsten Alpers, Glenn Pearson, Anne McKenzie

In 2007 we convened an Infectious Diseases Community Reference Group to inform the wider community about research conducted at ICHR around infectious diseases and for community members to provide researchers with their valuable input into research projects. This group consists of 13 members including 8 community members (of which 4 are Aboriginal), 2 researchers, 1 representative from the Western Australian Department of Health, 1 representative from the Vaccine Trials Group and 1 representative from the Institute for Child Health Research Consumer and Community Advisory Council. The current members of this group are: Glenn Pearson (Chairperson), Barry Combs, Bev Taylor, Helen Martin, Jane Jones, Karen Ziegelaar, Linda Gibbs, Maude Walsh, Natasha Indich, Patricia Nyaga, Rae Young, Trish Laitt, Anne McKenzie, Deborah Lehmann and Hannah Moore. This group met four times in 2011 and discussed the progress of the research projects associated with infectious diseases at ICHR.

Funders of the project: Jointly funded by the Meningitis Centre and NHMRC Project Grant #572590

NEONATAL IMMUNISATION WITH PNEUMOCOCCAL CONJUGATE VACCINE IN PAPUA NEW GUINEA

Deborah Lehmann, Anita van den Biggelaar, Pat Holt, in collaboration with Peter Siba, William Saila Pomat, Suparat Phuanukoonnon, John Reeder, Peter Richmond, Amanda Leach, David Smith, Ingrid Laing, Glenys Chidlow

Throughout the world an estimated 820,000 children die annually from pneumococcal disease, the majority in early infancy in third world countries. This study was designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in Papua New Guinean infants at 1-2-3 months of age and to find out whether neonatal immunisation in the first week of life would provide earlier protective antibody responses. The study is also assessing the impact of a 7-valent PCV (7vPCV) on early pneumococcal nasopharyngeal colonisation. We are investigating the development of mucosal and T-cell immunity to non-capsular pneumococcal protein antigens and how this may be affected by early onset of colonisation. We have assessed the impact of neonatal immunisation on humoral and cellular immune responses to concomitant vaccines (diphtheria toxoid, tetanus toxoid and measles) and whether PCV interferes with normal maturation of the immune system.

A total of 318 children were enrolled; 80% completed follow-up at 18 months of age. Results to date show

- No deleterious effect of neonatal 7-valent PCV (7vPCV).
- 7vPCV is immunogenic in PNG neonates and young infants.
- 7vPCV in a neonatal (0-1-2 months) or early infant (1-2-3 month) schedule primes for immunologic memory for 7vPCV serotypes with booster response to 23-valent pneumococcal polysaccharide vaccine (PPV) at age 9 months. Serotype-specific antibody concentrations are generally sustained to age 18 months.
- PPV induces good antibody responses for some non-PCV pneumococcal serotypes which commonly cause disease.
- 60% of infants were colonised with *Streptococcus pneumoniae* by age 1 month.
- 51 different pneumococcal serotypes have been identified in the upper respiratory tract.
- At age 9 months, 68-78% of pneumococci were non-7vPCV serotypes.
- PCV has limited impact on upper respiratory tract carriage in this population.
- Early pneumococcal carriage may result in enhanced disease susceptibility and suboptimal vaccine responses by modulating the development of pneumococcal immune responses.
- Analysis of cellular immune responses has shown that neonatal PCV vaccination is safe and not associated with immunological tolerance.

In an extension of this project IA Laing investigated the contribution of human genetic susceptibility to nasal bacterial carriage, development of immune/vaccine responses and the incidence of pneumonia in this population.

Preliminary results from investigation of associations between genotype and acute lower respiratory infections suggest that several genetic variants for known immune pathways may play a role in the frequency of lower respiratory tract infections in children in PNG.

At PathWest Laboratory Medicine WA multiplex PCR has been used to identify viruses in the nasopharynx of sick and healthy trial participants. Influenza virus A, respiratory syncytial virus and adenoviruses and detection of multiple viruses were more common during episodes of acute lower respiratory tract infections than when children were healthy.

Assays to measure mucosal immunity to pneumococcal polysaccharides are currently being optimized in the laboratories in Goroka.

Funders of the project: This study was funded by the NHMRC/Wellcome Trust International Collaborative Research Grant #303123

INVESTIGATION OF SEROTYPE-SPECIFIC ANTIBODY PERSISTENCE AND B-CELL MEMORY AT AGE 3 - 4 YEARS FOLLOWING 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE AT AGE 9 MONTHS IN PAPUA NEW GUINEAN CHILDREN PREVIOUSLY PRIMED WITH 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

Peter Richmond, Deborah Lehmann, Peter Jacoby, Anita van den Biggelaar in collaboration with Peter Siba, William Saila Pomat, Andrew Greenhill, Christine Opa, Gerard Saleu

Recently, concerns have been raised about the role of the 23-valent pneumococcal polysaccharide vaccine (PPV) in infants following priming with a pneumococcal conjugate vaccine due to a potential immunological hypo-responsiveness (i.e. a poorer immune response to subsequent immunisation or natural exposure). In PNG we have previously found that (a) PPV given from age 6 months onwards (without priming with conjugate vaccine) prevents death and severe morbidity due to acute lower respiratory tract infections up to age 5 years and (b) serotype-specific pneumococcal antibody responses are generally sustained up to age 18 months with a PPV booster at age 9 months following priming with 3 doses of 7vPCV. Nevertheless it is important to ensure the immunological safety of the PPV in infants.

This study aims to determine whether PPV given at 9 months of age:

1) provides enhanced persistence of antibody levels associated with protection from invasive disease at 3 to 5 years of age compared to unvaccinated controls

2) has an impact on the development of serotype-specific B-cell memory at 3 to 5 years of age

3) enhances antibody persistence and B-cell memory for those serotypes included in 7vPCV among children who received 7vPCV in early infancy

4) has an effect on long-term pneumococcal carriage in children primed or not primed with 7vPCV.

We are assessing immune function (by measurement of serotype-specific antibody

concentrations, opsonophagocytic antibodies and memory B-cell responses) and nasopharyngeal carriage at age 3-5 years prior to and one month after a challenge dose (0.1ml) of PPV in children who took part in the previous neonatal 7vPCV trial (described above) and in 150 age-matched controls.

We enrolled 130 of the children who had previously received PPV (primed or not primed with 7vPCV) and 150 controls.

Preliminary data show continuing high pneumococcal carriage up to age 5 years (>70%, predominantly non-PCV serotypes) irrespective of vaccination history, and high serotype-specific pneumococcal antibody concentrations. Preliminary analyses show no evidence of impaired antibody responses following a challenge dose of PPV.

Funders of the project: Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant

A STUDY TO DETERMINE THE SAFETY AND IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES IN PAPUA NEW GUINEAN CHILDREN

Deborah Lehmann, Andrew Greenhill in collaboration with Peter Siba William Pomat, Audrey Michael, Vela Solomon, William Lagani, Lea-Ann Kirkham, Peter Richmond, Trevor Duke, Megan Passey

Throughout the world an estimated 820,000 children die annually from pneumococcal disease, the majority in early infancy. While many industrialized countries have had pneumococcal conjugate vaccines in their routine immunisation schedules since 2001 and a 23-valent pneumococcal polysaccharide vaccine (PPV) has been shown to be efficacious in preventing death and severe disease from age 6 months onwards in Papua New Guinea (PNG), no pneumococcal vaccine is currently offered to children in PNG. The Global Alliance for Vaccines and Immunisation (GAVI) and the World Health Organization (WHO) have committed to the introduction of pneumococcal conjugate vaccine (PCV) for infants in GAVI-eligible countries (including PNG) and introduction of a PCV is planned for 2013.

The primary aim of this study is to determine whether PCV10 and PCV13 (which include 10 or 13 pneumococcal serotypes, respectively) are safe and immunogenic in Papua New Guinean infants for the serotypes in the respective vaccines.

This is an open randomised trial. We aim to enrol 200 children at age 1 month. Half will be randomised to receive PCV10 and the other half PCV13 a 1-2-3-month schedule. At age 9 months half in each group will be randomised to receive 23vPPV and the other half no PPV. To specifically address the possibility of hyporesponsiveness following PPV, all children will receive a challenge dose (0.1ml) of PPV at age 23 months and followed up 4 weeks later. Blood for antibody studies as well as and B- and T-cell responses will be collected at ages 1, 4, 9, 10, 23 and 24 months of age. Pernasal swabs will be collected at the same time points.

Recruitment into the study began in November 2011.

Funder of the project: Exxon-Mobil Governance and Public Affairs

Collaboration for Applied Research and Evaluation

ARE CHILD HEALTH SERVICES MEETING THE NEEDS OF WA PARENTS AND CHILDREN?

In collaboration with Child and Adolescent Community Health Policy Branch (WA)

Care Leads: Kim Clark, Judy Donnelly, Jordan Fisher and Tanyana Jackiewicz

The purpose of this research project is to assess whether the current child health services meet the needs of WA parents and identify why parents are not accessing child health services at key developmental ages (scheduled contacts at 18 months and 3 years).

The proposed study will have three interlinked components. The first is two 'community conversations' or forums that will respectively play a role in both informing and shaping subsequent qualitative and quantitative research and exploring final recommendations and suggested processes for managing any change. The second proposed component is a quantitative study of parents of children aged 0 to 4 years. It is proposed that the form of this study will be guided by both information gathered from the first community forum, by the approach taken with US Promoting Healthy Development Survey-PLUS (PHDS-PLUS) and the child health literature. Emphasis in this study will be given to identification of access to developmental health information, preferred sources of this information, and attitudes to child health services.

The third proposed component is a sequence of focus group sessions, with parents to be recruited from the quantitative study. Focus group questions will be informed by the first community forum and the literature.

Objectives of the proposed study

1. A diverse range of parents/carers are involved with and inform research directions and lines of inquiry so as to ensure that the research study reflects the priorities and concerns of the WA community.

2. A diverse range of parents/carers are invited to participate in the research study as survey respondents, interview and focus group participants, so that the felt needs of WA parents for child health information and services are identified.

3. The barriers and facilitators to WA parents accessing and engaging with child health services, particularly the scheduled contacts, are identified.

4. Strategies and processes to improve the delivery of child health services are identified.

In 2011, a project reference group was formed to discuss a review of processes and develop questions for surveys, interviews and focus groups. The scientific protocol and

ethics application was submitted and ethics approval via the DoH HREC has been received. The questionnaire design is complete and the instrument was trialled before use in the field. Field work has progressed, with approximately two thirds of the planned survey data actually obtained. Field work, however, stalled in December as a consequence of insufficiency of the sample of contact numbers obtained from the DoH data linkage group as a result of a poorer-than-expected success rate in contacting parents. Survey data is expected to be delivered in March 2012.

A Community Conversation was undertaken in October in Mullalloo. Planning for an additional conversation to be undertaken in Kwinana is underway. Focus group questions and format has been developed. A trial focus group was undertaken in December and the results of this will be used to guide the approach to be taken with subsequent focus groups. A report on this was sent to the project reference group which will meet again in February 2012 to approve to approach to be taken with focus group research. Focus groups are planned at the completion of the survey component of the research.

The project output will be a comprehensive report into the provision of well-child health information and services to Western Australian parents of children under 5 years old. This report will include discussion on:

- The expressed needs, priorities, barriers and facilitators to accessing child health information and services (particularly at key developmental stages) for WA ;
- Processes and modes of child health service delivery that enable increased parental engagement with, and responsiveness to, evidence-based child health information and guidance;
- Options for improving accessibility and acceptability of well-child health information and support to WA parents.

Funders of the project: Department of Health

TRIPLE-P PARENTING PROGRAM: LONG-TERM OUTCOMES AND ECONOMIC BENEFITS

In collaboration with Child and Adolescent Community Health Policy Branch

CARE Leads: Grant Smith

This research project will evaluate the Triple-P Program's long term effectiveness, using data collected in the initial effectiveness trial and data on the children and their family up to 13 years following the intervention (children of parents enrolled in the program are now at least 16 years old).

The WA Triple-P study database will be linked to a number of administrative databases (e.g. education, health, mental health, justice, child protection, drug and alcohol, mortality) to determine whether the program was associated with better long-term outcomes for children.

The project will also use costing algorithms to determine how these outcomes translate into costs/savings to the WA government and develop an overall cost-benefit model of the Triple-P Parenting Program.

The specific hypotheses for this research are:

At the age of 16-17 years, children whose parents received the Triple-P Parenting Program will have:

1) lower number of hospital/emergency department admissions

2) lower levels of teenage pregnancy

3) lower levels of school absenteeism and lower risk of suspension/expulsion from school

4) higher performance on literacy and numeracy tests

5) less contact with the justice system

6) less contact with the mental health system

7) lower incidence of problematic drug/alcohol use

It is hypothesised that improved outcomes associated with the Triple-P program will translate into significant cost savings to the Western Australian government and that the delivery of the program will be associated with a net positive economic impact.

A reference group has been formed, ethics documentation prepared and feedback received from the DOHWA Ethics has been received and addressed. The correspondence with the committee has indicated that approval will be given out of session. Data linkage will commence immediately following this approval. The project is also currently awaiting approval from the Department of Corrective Services Ethics Committee (this approval is not required for linkage to begin and will be received whilst data linkage is being conducted). The literature review has commenced and the introduction and methods sections of the report are currently being prepared. Whilst awaiting ethics approval the personal information from the WA Triple-P Evaluation Database has been extracted and formatted to provide to the Data Linkage Unit. Some cleaning of Triple-P database was required (removal of duplicate cases, ID of non-response/ missing items). In preparation for receipt of linked data and data analysis, the distribution and completeness of key covariates is currently being examined (and key literature examined) to determine what will be included in analyses.

A report will be prepared for the Department of Health, WA outlining the key findings of the research. An article outlining the results of the research for submission to a scientific journal will also be prepared. At this stage, these outputs will be delivered by December 2012.

Funders of the project: Department of Health

THE DEVELOPMENT OF A NOVEL ANTENATAL EDUCATION PROGRAMME FOR FIRST-TIME OBESE MOTHERS-TO-BE ON THEIR INTENTION TO MANAGE THEIR GESTATIONAL WEIGHT GAIN AND FOSTER A HEALTHY LIFESTYLE

In collaboration with Professor Yvonne Hauck (KEMH)

Dr Lisa Gibson will lead the project with support from Kim Clark and Tanyana Jackiewicz

The aim of this project is to develop an evidence-based and field-tested antenatal care and education package based on the 'Centering Pregnancy' model that is acceptable to pregnant women with a body mass index (BMI) of ≥30

kg/m2. The package is to be designed with the goal of positively influencing participants' intention to manage and thus minimise their gestational weight gain whilst fostering the adoption of a healthy lifestyle.

The project is consistent with the Department's strategic objectives and would progress the following strategic objectives of the Western Australian Health Promotion Strategic Framework 2007-11 and the National Preventative Health Strategy (2009), that is:

- Ensure women planning pregnancy and pregnant women receive information, education and support to reduce lifestyle risks of excessive weight and poor nutrition.
- Provide consistent and clear information to parents to support them to establish appropriate eating and physical activity patterns in children and to better understand the risks of unhealthy weight in early life through targeted interventions for parents.

The overall project will comprise:

- Research and consultation: Formation of a consumer reference group to inform the type of information required and how to present it within a group antenatal education package.
- Development of an antenatal education package: Development of approximately 4 education sessions along with support materials and resources for the target group to cover healthy family lifestyle issues in the pre-natal and post-natal periods.
- Preliminary trial of antenatal package content with women to assess acceptance of material covered and method of delivery.
- Evaluation of the intervention with the primary target group through conducting focus groups post each trial session.

The project objectives are:

Objective 1: Review of evidence on interventions that have potential application in addressing obesity among pregnant women.

Objective 2: Design of a draft antenatal care and lifestyle education package for obese mothers-to-be.

Objective 3: Pilot-testing of each session in the maternal obesity education package with members of the target group recruited from KEMH.

During 2011 the following has been achieved:

Formation of steering committee and project managers

The project's steering committee is comprised of Yvonne Hauck (Curtin University), Anne Rae (KEMH), Hanna Burbidge (KEMH), Kim Clark (TICHR), Barbara Loury (KEMH), Lisa Gibson (TICHR) and Ms Tanyana Jackiewicz (TICHR). The project managers, Joan Jones (KEMH), a midwife and Anna Fletcher, a dietitian (KEMH) meet regularly with the steering group to discuss and review project progress.

Ethics Approval

The project gained ethics approval to recruit current outpatients from KEMH and conduct the session trials at KEMH from the WNHS Ethics Committee. This was approved on October 4, 2011.

Governance approval for consumer reference group formation

The project gained approval by King Edward Memorial governance committee to form a consumer reference group using current and recent outpatients. This was approved in October 2011.

Formation and meeting of the consumer reference groups

After consulting with Anne McKenzie (Consumer Research Liaison Officer, UWA) to determine the method of forming such a group, eligible women (BMI ≥ 30 kg/m2) were contacted and recruited. Two consumer reference groups were formed; one south of the river (Rockingham) and one north of the river (Joondalup). In November 2011, a focus group/morning tea was conducted with each of these groups to discuss the maternity experience of obese women, how their care could be improved, how they could be more supported to achieve a healthy gestational weight gain and the perceived acceptability of a group-based educational package.

Preliminary literature review

A literature review has been conducted to establish evidence-based content to inform the development of each session in the intervention package for obese mothers-to-be.

Participant recruitment plan

Through meeting with the KEMH clinic referral triage midwife, we have formed a recruitment plan involving identification of eligible women using the hospital patient management system.

The next steps to be completed in 2012 are:

Drafting of package content

Using the literature review findings and the feedback from the consumer reference groups each session will be drafted. The proposed content for each session will be reviewed by the consumer reference group to refine approaches and to obtain guidance on the acceptability of the proposed content and delivery methods.

Recruitment of participants

Recruitment will begin in February 2012.

Trial and re-trial of antenatal session content according to focus group outcomes

Trial of the sessions will begin in March 2012. Post each trial session a focus group will be conducted to evaluate the acceptability of the content. Each session will be re-trialled in the case of significant changes/improvements.

Funders of the project: Department of Health

THE PSYCHOSOCIAL DETERMINANTS OF HEALTH OUTCOMES IN YOUNG CHILDREN WITH CYSTIC FIBROSIS (CF)

In collaboration with Dr Tonia Douglas and Catherine Gangell from Cystic Fibrosis Research Group at PMH, CARE Leads: Grant

Smith

The primary aim of this pilot study is to gather data to inform the design and implementation of a longitudinal research project examining the relationships between psychosocial factors and the progression of CF lung disease.

To meet this aim, a primary cross sectional study of preschool children diagnosed with CF through NBS and their families in Western Australia will be conducted to gain insight into the relationships between psychosocial factors and disease progression. Information will be gained through one-to-one interviews of parents of children with CF and through self-administered questionnaires.

The specific objectives for the project are:

- To identify the cross-sectional relationships between child health measures (designed to measure the progression of CF), and the following psychosocial measures: family functioning, parental mental health, parental reflective functioning, and dyadic relationships.
- To use novel and sensitive techniques to detect and quantify disease progression/ severity in young children with CF.
- To determine the value and precision of each of the psychosocial instruments as correlates of health status in early life and inform the choice of instruments for the longitudinal study.

Ethics documentation has been prepared and tools have been designed. HREC has yet to approve the study due to essential changes to the study protocol that required resubmission of the application. A literature review has been prepared.

Findings of this primary cross-sectional study will be presented to the CF clinic at Princess Margaret Hospital and interpreted within the context and limitations of the study design. We anticipate that results will inform the CF multidisciplinary team of significant links between disease progression and specific psychosocial domains within this population of children. We anticipate that this information will provide the foundations for design of psychosocial screening tools and intervention strategies on a local level, which will be further developed with the results of the longitudinal study.

Funders of the project: Department of Health

RESPIRATORY SYMPTOMS IN CHILDREN WITH CEREBRAL PALSY

In collaboration with The Centre for Cerebral Palsy and Associate Professor Eve Blair (TICHR). CARE Leads: Grant Smith

The aim of this study is to determine the prevalence of respiratory problems in children and adults with CP in Western Australia. This information will be used to identify and intervene as early as possible in order to prevent serious respiratory problems from developing.

The objectives of this study of children and young adults with CP are to determine:

1) the prevalence of respiratory symptoms and morbidity,

2) the risk factors for severe respiratory problems,

3) the prevalence of known risk factors for severe respiratory problems, and

4) the relationships between selected risk factors, respiratory symptoms and respiratory morbidity.

The study will produce prevalence data on respiratory symptoms, morbidity and risk factors for children, adolescents and young adults with CP by severity of impairment, age and feeding method used. Such data are not currently available in the published literature. The data can be used for early identification and intervention in order to prevent the development of serious respiratory problems.

The project will provide a method for tracking changes in these problems over time with a view to identifying early risk factors and protective factors for later serious respiratory problems.

In 2011, a project reference group was formed with considerable discussion of questions in questionnaire amongst group members. An application has been submitted to the PMH Health Research Ethics Committee (HREC) for permission to amend the questionnaire and approval was provided by the PMH HREC in October 2011. Scientific protocol and ethics application has been submitted and ethics approval via the DoH HREC has been received. The questionnaire has been piloted and finalised with the development of an electronic online questionnaire. A recruitment poster has been prepared and printed as well as information sheets and final questionnaire tool (6 versions).

A mailout of invitation letter to be involved in the study has been sent to clients who fitted the eligibility criteria (N=627). A media release has been prepared and submitted to the TCCP newsletter 'Brand News' to assist in recruitment. A mailout of information sheet and questionnaires to TCCP clients who had not opted out of study (N=568).

Data collection has commenced and as at 31 December 2011 the project has collected 100 completed questionnaires (~18% response rate). Progress is on track for the delivery of the final report by June 2013.

Funders of the project: Department of Health

LONG-TERM OUTCOMES ASSOCIATED WITH THE USE OF STIMULANT MEDICATION IN THE TREATMENT OF ADHD: OUTCOMES AT 17 YEARS OF AGE

In collaboration with Craig Russell (MICADHDWA), Brad Jongeling (Child Development Service) and Lou Landau (DOH). CARE Lead: Grant Smith

This project will replicate the methodology used in the report: *Raine ADHD Study: Long-term outcomes associated with stimulant medication in the treatment of ADHD in children*[1]. However, where the previous report examined outcomes measured at the 14-years of age, this project will examine outcomes measured at 17 years of age.

Specifically, this project will aim to use longitudinal data from the Raine Study to examine the long-term associations between stimulant medication-use during childhood

and adolescence and a number of outcomes for children with ADHD. These outcomes, measured at 17 years of age, include: Social, Emotional, Educational, Growth Measures, and Cardiovascular Function. The 17 year follow up also provides an opportunity to examine addition variables such as employment and employment related training, if these additional variables are available. It is hypothesised that different patterns of medication use will be associated with different outcomes.

Approval from the Raine Executive Group was received in October 2011 for both stages of the research. The delay was a result of additional time spent on ensuring appropriate support and engagement from all stakeholders in this project. The use of medication for the treatment of ADHD is a controversial topic and therefore a considerable amount of time was spent ensuring that the analysis plan addressed all concerns of the stakeholders before the application was submitted to the Raine Executive Group. Data is currently being extracted.

The timeline for the delivery of the project final report has been amended to reflect delays as a result of our engagement strategy with all relevant stakeholders in the project. Progress is now on track for the delivery of the final report by the end of June 2012 and a paper by the end of August 2012.

Funders of the project: Department of Health

INTEGRATED EARLY YEARS SERVICES PROJECT

In collaboration with Child and Adolescent Community Health Policy Branch

CARE Lead: Kim Clark

This project seeks to characterise whether there are factors within the design and operation of integrated early years services that lead optimise developmental outcomes for pre-school children and best support their families. An output of the project will be a framework for assessing the quality of early years service integration. This was to be developed via a detailed analysis of the literature, interviews with early years service staff in a range of metropolitan and rural settings, and discussions with parents and other stakeholders. The framework will enable the Department of Health to better assess the potential benefits of service integration and consequently aid policy making.

Proposed tasks in the development of the quality and evaluation framework included an analysis of the literature, focus groups and key informant interviews with a range of staff working in integrated early years services centres across WA, and focus groups and key informant discussions with parents and community stakeholders regarding early years services.

Field work for the project was to include site visits to 4 rural locations that have integrated early years services in operation (site selection under the direction of WACHS).

A steering group has been formed and has met to endorse the quality audit/checklist review process; interpret quality audit/checklist data. A report has been prepared to the steering/reference group on quality audit/checklist results and obtain agreement on audit recommendations. Planning with both WACHS and CACH led to the identification of 3 rural sites for assessment as part of the project and 1 metropolitan site.

The report format agreed by the project steering group will be a manual for the development and evaluation of integrated early years services. A review/synthesis of integration literature has been completed. Ethics approval for interviews was obtained through the ECU Research Ethics Committee. Focus groups and key informant discussions have taken place. The focus group and key informant data has been including in a report to steering group. This workshop has taken place and a draft report to steering group for endorsement of program logic and evaluation recommendations has been prepared.

Funders of the project: Department of Health

INFANT FEEDING IN WESTERN AUSTRALIA: ESTABLISHING A BASELINE AND EVALUATING THE WA DEPARTMENT OF HEALTH'S BABY FRIENDLY HEALTH INITIATIVE POLICY (BFHI)

Grant Smith and Tanyana Jackiewicz

To undertake a state-wide population-representative survey with the aims of 1) determining the relationship between hospital practices (and community services) and breastfeeding practices 2) identifying whether the DOH BFHI policy rollout was associated with improved infant feeding practices in WA, and 3) obtaining a reliable baseline measure on prevalence of breastfeeding in WA.

The initial (baseline) survey of 1054 mothers with children aged 9 months across Western Australia was conducted in 2010 using computer assisted telephone interviewing with the assistance of the ECU Survey Research Centre. Mothers were asked about their experiences in hospital that relate to BFHI practices; they were asked about their infant feeding practices including duration, introduction of formula and other liquids and the introduction of solids. Finally they were also asked about their experiences with community services aimed to improve infant feeding practices.

A report has been prepared that provides a description of the results collected via Phase I of a project aimed at evaluating the WA Department of Health's Baby Friendly Health Initiative policy (the WA Hospital Breastfeeding Policy) rollout. The report provides 2010 data for infant feeding practices in WA and experiences of Baby Friendly Hospital Initiative (BFHI) practices in hospital for mothers who gave birth prior to the introduction of the WA Hospital Breastfeeding Policy.

These results will be compared to data to be collected in 2012 as a means of evaluating the WA Hospital Breastfeeding Policy. The infant feeding data gathered indicated that a large portion of infants did not receive the optimal infant nutrition during the first six months of their life. Whilst almost all WA mothers initiated breastfeeding their infant (98.3%),

only 67.1% of infants were still receiving some breast milk at six months of age.

The duration of 'full' breastfeeding (providing no source of nutrition other than breast milk or water) of WA infants was examined and the following key baseline results gathered:

- 69.9% of infants were 'fully' breastfed beyond the first week of life
- 45.9% of infants were 'fully' breastfed up to four months of age
- Only 12.6% of infants were 'fully' breastfed up to six months of age

The duration of exclusive breastfeeding (providing no source of nutrition other than breast milk) of WA infants was examined and the following key baseline results gathered:

- 68.7% of infants were exclusively breastfed beyond the first week of life
- 34.6% of infants were exclusively breastfed up to four months of age
- 8.7% of infants were exclusively breastfed up to six months of age

A scale was developed to measure a mother's experience of Baby Friendly Hospital Initiative (BFHI) practices. This scale indicated that, on average, mothers have a high experience of BFHI practices in WA hospitals. Out of a possible 40 points (indicated a high BFHI experience) the average experience of WA mothers was 33.1.

There was a significant proportion of mothers, however, who reported a hospital experience that was not in line with BFHI practices; indicating room for improvement in some WA hospitals.

Mothers who had greater experience of BFHI practices whilst in hospital were significantly more likely to 'fully' breastfeed their infants to the age of four months. This relationship remained significant after adjusting for key sociodemographic covariates.

Younger maternal age, lower levels of maternal education, being a single mother, and giving birth to first child were all associated with lower percentages of mothers reporting they had breastfed their infant to four months of age. Infants residing in the Northern and Southern regions had the highest percentage of infants 'fully' breastfed to four months of age. The lowest rates were observed in the South Metropolitan and Central areas.

'Full' breastfeeding and 'full' breastfeeding with occasional supplementation indicated that there was a significant number of infants who received formula in the first week of life (usually in the hospital, presumably by medical indication) but were nevertheless considered to be 'fully' breastfed to four or six months. A comparison of the durations of true exclusive breastfeeding and exclusive breastfeeding with occasional supplementation yielded similar observations.

Phase II

The survey will be repeated in 2012 to determine whether the rollout of the WA Hospital Breastfeeding Policy is associated with statistically significant increases in BFHI Experiences of WA mothers and the proportion of infants 'fully' and exclusively breastfed to the ages of four and six months.

Funders of the project: Department of Health

DELIBERATE SELF HARM IN WESTERN AUSTRALIA

Grant Smith and Dr Tracy Reibel

This project will use qualitative and quantitative methods to examine the effectiveness of the various referral pathways (on separation from EDs) with regard to reducing the likelihood of readmission. The qualitative element of the project will involve interviews with first-time DSH ED clients and clients who have been admitted to ED for DSH injuries multiple times. Elements of the referral pathway that were helpful and those that were not helpful in preventing further episodes of DSH will be identified. The quantitative aspect of the project will involve the collection of data on referral pathways data from the written ED records of DSH clients. This data will be linked to Data provided by the Developmental Pathways Project (specifically the WA Emergency Department Data Collection, the Hospital Morbidity Data Collection, and Mortality) to determine which referral pathways are associated with a lower likelihood of repeat DSH admission (or suicide).

In 2011, support was sought from hospitals with EDs in the Perth Metropolitan area. The majority of these have agreed to take part in the research following approval of the projects by Human Research Ethics Committees. The applications for ethical review have been submitted to the Princess Margaret Hospital Scientific Advisory Sub-Committee and are currently under review by the Human Research Ethics Committee. Both aspects of the project rely on receipt of linked data through the Developmental Pathways Project at the Telethon Institute for Child Health Research. Our expression of interest has been approved by their governance group; however, this data will not be available until 2012. Following receipt of the DPP data, linkage to the newly gathered data from the ED records will take approximately 6 -8 months through the WA Data Linkage Unit. Given the time taken for data receipt and linkage, it is expected that this project will be completed by December 2012.

Funders of the project: Department of Health

IMMUNISATION CONSENT RESEARCH PROJECT

CARE Leads: Kim Clark, Judy Donnelly, Jordan Fisher and Tanyana Jackiewicz

The output of the research will be evidence based recommendations on the design of immunisation consent resources and procedures for use in WA.

This research is intended to engage Western Australian parents and immunisation providers to inform the development of both improved immunisation consent resources and a protocol for use by WA immunisation providers. The project has a sequence of stages. The scope of the current project entailed the following:

(1) Audit and Literature Search

This stage of the project was to examine the current state of immunisation consent, giving emphasis to the types of resources used by Australian and overseas providers. The literature

was to be examined to highlight discussion of, and research into, immunisation consent procedures for parents with young children. An audit of protocols used in WA by different service providers, in both metropolitan and regional areas, was also to be undertaken.

(2) Experiences, perceptions and recommendations of consumers

This stage of the project was to explore the experiences and perceptions of Western Australian parents regarding the consent process followed with their children's immunisation. Qualitative and quantitative methods of data collection were to be undertaken to establish an indication of the views that Western Australian parents have of current approaches to consent as well as their opinions about improvements in this area.

The study has been overseen by a reference group and has ethics approval via the DoH Health Research Ethics Committee (HREC). The reference group played a substantial role in all aspects of project development.

The project literature review has been completed. Questionnaire design for the survey aspect was completed and the instrument was trialled before use in the field. Subsequently, field work was completed and study data is currently being analysed for reporting. A "Community Conversation" was undertaken and reported upon. A further conversation will be held in February 2012. An audit of current practice has been completed and a report written on this aspect. An online survey of WA immunisation providers has also been completed and data from this survey will be analysed in February 2012.

Focus group research for the project will be undertaken in Feb-March 2012.

Funders of the project: Department of Health: Communicable Disease Branch

INNOVATIVE HEALTH SERVICES FOR HOMELESS YOUNG PEOPLE (IHSHY) EVALUATION

Dr Tracy Reibel and Tanyana Jackiewicz

The purpose of this research was to identify the attributes of WA IHSHY services, by asking the users of the services and those who work within the service, what makes these services able to work successfully with marginalised young people with complex needs, including Indigenous young people. Five IHSHY services were involved in the evaluation including: Perth Street Doctor; Fremantle Street Doctor, Adolescent Mothers Support Service, RUAH Young Women's Program and Hills Community Support Service.

Qualitative research is particularly useful in understanding the socio-cultural context of complex behaviours particularly in marginalised populations such as homeless youth and an informal interview based structure was used in this evaluation as the most appropriate means to elicit information from at risk and homeless youth. A total of 49 interviews were conducted with young people (15-24 years) recruited across 5 IHSHY services in the Perth metropolitan area. In addition, a total of 18 interviews were conducted with service providers within these services.

This study confirmed that young people in metropolitan Perth share many of the views and opinions of their peers reported in other studies. That is, what makes IHSHY services accessible to young people is that they either offered an outreach/home visiting approach or provided transport as required (for intensive social support models) or in the case of Street Doctors, these services were located in places that were easy for young people to access such as on transport lines or close to community centres. The client results showed that young people access IHSHY services because they are conveniently located or offered a home visiting/outreach service, which makes access straightforward. Other factors include clients not having to incur a cost to receive the service, and importantly, the informal and relaxed atmosphere of services. Aboriginal clients particularly referred to feeling secure accessing Fremantle Street Doctor as it did not require them to sit in unfamiliar or unwelcoming places such as doctors surgeries. Unbooked appointments or having the service come to them, particularly when public transport is not available, was also a factor in ease of access to these services by both Aboriginal and non-Aboriginal clients.

In regard to acceptability for young people, the fact that the services are of no cost, have an informal and relaxed atmosphere was a draw card for young people, particularly in relation to the drop in nature of the Street Doctor mobile primary care 'clinics'. Aboriginal clients reported that they felt accepted by the staff and that they felt understood. For the outreach services, the approach of the workers in not being too pushy, and being accepting of the clients own situation was also important to young people. The young people also reported that they had trust in the service personnel and were confident that their confidentiality was protected. At the same time they did require continuity of service providers and were quick to point out that relationships and trust are important. Most young people talked about IHSHY services and the service personnel as being easy going, fun and informal with non-judgemental attitudes. The area that remained problematic for many young people was in accessing mainstream services either because they felt they did not need the services or because they were not confident in keeping appointments or approaching these services without an advocate.

The service personnel interviews provided for an in depth perspective of the services; and providers noted that for their services to be very accessible to young people – location is important. There was reflection from Street Doctor personnel that integration with other community services is an essential aspect of building relationships with local Aboriginal communities in particular. Co-location provides an opportunity to expose young people to other services but also makes the Street Doctor services visible in places where young people are known to frequent. Service participants noted their respect and admiration for the young people who use their services. To understand what drives their commitment, we asked service providers

what qualities they think are imperative for staff to have to work in their type of service. Not surprisingly, the qualities or attributes service personnel identified were similar to young people's views on provider qualities. These are, being non-judgemental, philanthropically inclined, passionate, respectful, easy going, with a sense of humour and empathetic with the client group. Additionally, the service personnel discussed the necessity to work as a team to build relationships with their clients acknowledging that the work is challenging. Even though the work is demanding, unpredictable and at times overwhelming, it was emphasised that being in a team and making even a small difference in people's lives makes the work worthwhile. A combination of team work and working with the clients with knowledge and empathy was noted as essential to making the services work so that young people will return.

Clients were asked to identify any improvements to services and a number of young people from the Street Doctor sites recommended more access to warm clothing and coffee, onsite pharmacy and free scripts, and more services in more locations. Many clients also asserted the need for a 24 hour/7 day a week availability of services, particularly drop-in centres for short term, safe accommodation, showers and meals. Clients from outreach services tended not to suggest any improvements when interviewed, which was taken to mean that the service they were provided with was sufficient for their needs. Importantly, however, and a key finding in this research, is that young people identified the need for access to counselling, mental health and psychology services, as well as drug and alcohol agencies, youth workers and childcare. Mental health issues were a common theme for both young people and service personnel.

Importantly, access to acceptable and accessible mental health has been identified in this evaluation as a prevalent issue with homeless and at risk young people. It is clear that there is a need for better integration between youth oriented mental health services and IHSHY services, with defined referral pathways to ensure timely engagement, but also for psychologists and counsellors to be incorporated as part of the IHSHY service model multidisciplinary teams. This aspect of providing holistic care to disadvantaged youth is one of the most resource poor of all service gaps. The lack of referral pathways to appropriate mental health services and indeed the lack of these services for youth is a key area of need identified by both clients and service personnel and fully supported in the literature and is highlighted here as a significant barrier to addressing homeless and at risk youths' full spectrum of health needs.

Funders of the project: Department of Health

AN EVALUATION OF THE IMPLEMENTATION AND DISSEMINATION PROCESSES FOR THE WESTERN AUSTRALIAN OPERATIVE DIRECTIVE FOR CO-SLEEPING

Dr Jenny Dodd

This evaluation assessed the effectiveness of the implementation and dissemination processes of the WA Operational Directive State wide co-sleeping/bed-sharing policy (OD). The research idea originated from the Women and Newborns Health Network (Department of Health) in consultation with the Telethon Institute for Child Health Research. The purpose of the evaluation was to assess the effectiveness of the implementation and dissemination processes of the OD across state government maternity units, private hospital maternity units, child health and community health services in Western Australia. This was achieved through a multi method research design involving service audit, interviews and focus groups with health workers and interviews with WA mothers. The evaluation also included the identification of other sources of co-sleeping information, policy guidelines and directives used across maternity and child health services. Key findings of the evaluation included the barriers and facilitators for health workers in providing co-sleeping information and highlighted the complexities and dilemmas in interpreting the intent and practice of the OD. Health workers and WA mothers informed suggestions and recommendations for developing and disseminating co-sleeping education that responds to the diverse cultural and life-style backgrounds of WA families.

Overall the evaluation has shown that generally the OD is well disseminated throughout government and private maternity units, however, is less well distributed or known about in community health and Aboriginal Community Controlled Health Organisation (ACCHO) settings. The manner in which the OD has been interpreted and responded to by the health professionals/workers in this evaluation has shown that the implementation of its recommendations seems on the surface quite effective. Whilst many women and health professionals know and understand what the key messages about co-sleeping are, there are multiple reasons for non-compliance or only partial adherence to the OD recommendations. These may include the philosophical beliefs and attitudes about bonding and attachment by health professionals and women, pragmatic considerations such as lack of sleep, limited access to material resources such as cots, overcrowded living conditions experienced by mothers and cultural beliefs (co-sleeping is normalised) by both health workers and mothers. Some health professionals and women also question the scientific basis for the OD and require more clarity around the absolute risk of co-sleeping deaths when all other risk factors have been taken into account. The evaluation also identified key areas of confusion and information gaps that are not directly addressed by the OD, particularly around the issues of the use of safe sleeping aids and side cots, wrapping, stroller sleeping and mattress fumes. These were all issues identified by both health professionals and mothers as requiring clarification and the development of appropriate information.

Funders of the project: Department of Health

TO INVESTIGATE THE RESOURCES AND SUPPORT AVAILABLE FOR WOMEN (INCLUDING ABORIGINAL AND CALD) ACCESSING MATERNITY SYSTEM SERVICES, WHO ARE AT RISK OF DOMESTIC VIOLENCE

Dr Jenny Dodd

This research project reviewed and mapped the current processes, guidelines and protocols that are in place that respond to pregnant women, at risk of family domestic violence (FDV), who are accessing maternity system services in Western Australia. The referral pathways that are utilised was identified through analysis of guidelines and protocols used by a range of maternity health system services and through interviews with Health professionals/workers and Social workers.

A mixed methods approach was used including policy and literature overview, audit, focus group and interviews with a range of health and community sector workers across health, child protection, immigration, communities, legal, drug and alcohol and housing sectors. These methods resulted in a comprehensive and in-depth overview of the key issues and concerns for pregnant women at risk of FDV and the maternity service workers who they come in contact with. The methods used enabled the identification of processes and strategies that are currently working well as well as those requiring further development.

This project reported that formal and informal screening methods are used by a range of government, private and community-based maternity services. Formal methods are less useful for Aboriginal and CaLD women and health workers recommended the use of informal and trust building processes for these. Referrals to external support services from these different methods of screening are effective when they occur, but there is also unmet demand for counselling and appropriate accommodation services particularly for young pregnant women, Aboriginal women, CaLD women (particularly those on accompanying and/or student visas) and women living in rural areas.

Further, well established referral pathways are reported between some major government maternity units in metropolitan Perth and social worker support, counselling, domestic violence advocacy and young women's accommodation and support services. These are generally less developed in some regional and rural areas particularly where communities may be dispersed. However, some smaller regional towns have good integration and relationships between maternity services and external services, although demand for services is often greater than availability and are more likely to be subject to workforce shortages and mobility.

The majority of maternity health services workers report feeling generally supported by their management, however, also identify that FDV professional development, space for confidential screening and "burn out" of health professionals are issues requiring attention. The majority of health workers describe FDV guidelines and screening tools as useful starting points, along with the ability to refer pregnant women to social workers and counsellors in the first instance, as most important. The majority of health workers feel constrained by mandatory reporting requirements and require more support from management in negotiating and discussing cases with the Department for Child Protection, including professional development and emotional support. There are some areas where maternity health services and community support services such as housing and counselling are already working well. However, there are also areas where increased collaboration and integration are required particularly in meeting the needs of these women:

- Young women – accommodation, counselling, legal representation, substance misuse.
- Aboriginal women – culturally relevant responses, information, accommodation, support services for men, substance misuse and increased ability to remain in their own homes.
- Culturally and linguistically diverse women – culturally appropriate information, support and services for women on accompanying and/or spousal or student visas, access to publicly funded health, housing and income support services, culturally appropriate information and responses to contraception, termination and unwanted pregnancies.

Overall, this research project reminds us that there is no one solution, screening tool or process that is applicable to all pregnant women at risk of FDV. Family and domestic violence is a complex area and ensuring that the needs of pregnant women in all their diversity are met often requires referrals to a wide range of health, community and support services outside the immediate remit of maternity services.

The results of this research process has led to the formation of inter-agency leadership group with representatives from the range of government and community agencies to consider how pregnant women at risk of FDV can access additional services and support both within and external to the maternity health services.

Funded by the Department of Health

Developmental Pathways in WA Children Project

Fiona Stanley (University of Western Australia (UWA), Telethon Institute for Child Health Research (TICHR)); Helen Leonard (UWA, TICHR); Nicholas de Klerk (UWA, TICHR); Jianghong Li (Curtin University of Technology, TICHR); Natasha Nassar (UWA, University of Sydney); Stephen Zubrick (UWA, TICHR); Catherine Taylor (UWA, TICHR); Amanda Langridge (UWA, TICHR); Eddie Bartnik (WA Mental Health Commission); Cheryl Gwilliam (WA Department of the Attorney General); Ian Johnson (WA Department of Corrective Services; Tim Marney (WA Department of Treasury and Finance); Karl O'Callaghan (WA Police); Sharyn O'Neill (WA Department of Education); Grahame Searle (WA Department of Housing); Ronald Chalmers (Disability Services Commission WA); Jenni Perkins (WA Department for Communities); Cliff Weeks (WA Department of Indigenous Affairs); Diana Rosman (Department of Health WA); and Kim Snowball (Department of Health WA)

The Developmental Pathways Project is a landmark project taking a multidisciplinary and holistic approach to investigate the pathways to health and wellbeing, education, disability, child abuse and neglect, and juvenile delinquency outcomes among Western Australian children and youth. To achieve this, researchers from the Telethon Institute for Child Health Research and the University of Western Australia have been working in collaboration with a number of state government departments, including the WA Departments of Health, Education, Child Protection, Corrective Services, Communities, Indigenous Affairs, Treasury and Finance, Housing, Attorney General, the Disability Services Commission, the Mental Health Commission, and WA Police. The project has established the process of linking together de-identified longitudinal, population-based data collected and stored by a large number of these WA government departments and the Telethon Institute, to create a fantastic cost-effective research and policy planning/evaluation resource. The project has also established a Directors' General Steering Committee who meet twice a year to discuss how to best use these joined up data and joined up agency resource. In 2011 the project also established a Consumer and Community Reference Group who meet four times a year to provide an oversight role for governance, standards and practices relating to the project from a community perspective.

The linked data are being used by researchers and the respective departments to identify multi-level and early determinants of developmental outcomes and the interrelationships among them. Through the effective communication of the research findings, future government agency policies, practice and planning initiatives will be more preventative, culturally appropriate and cost efficient, and we have encouraged cross-agency collaboration to ensure improved health, well-being and development of children and youth, their families and their communities.

Funders of the project: The Developmental Pathways Project was made possible by the generous cash and in-kind contributions made by all of the collaborating organisations and government departments, which has been matched by the Australian Research Council (ARC) through two consecutive ARC Linkage Project Grants.

The Developmental Pathways Project supports several postgraduate students and postdoctoral fellows, to conduct individual research projects which answer specific research and policy relevant questions within and across the themes and scope of the overall project.

CHILD ABUSE AND NEGLECT

Conducted by Dr Melissa O'Donnell

Dr Melissa O'Donnell is an NHMRC Early Career Fellow and a Psychologist who completed her PhD in 2009 through the University of Western Australia. Her research uses longitudinal population data provided through the Developmental Pathways Project. This administrative data is being used to: investigate emergency department presentations and hospital admissions related to child abuse and neglect; determine the mental health and juvenile justice outcomes of children who have contact with the child protection system; and investigate the child, family and community characteristics which increase or reduce vulnerability to child abuse and neglect.

ABORIGINAL HEALTH RESEARCH

Conducted by Glenn Pearson

Glenn Pearson, a Noongar from Western Australia, and Manager of Aboriginal Health Research at the Institute, is completing his Doctorate on the Developmental Pathways Project. His qualitative research PhD project explores how the delivery of health, education and child protection services provided by the WA State Government to Aboriginal clients is mediated by the perceptions Non Aboriginal and Aboriginal people hold of themselves and each other in the provision and receipt of these services.

Conducted by Jocelyn Jones

Jocelyn Jones is completing her doctorate through the Developmental Pathways Project. Her project is titled 'Exploring the pathways to contact with juvenile justice in Aboriginal and Torres Strait Islander children: developing a profile of the risk and protective factors to support a strategy for change'. Using linked longitudinal population data provided through the DPP this project seeks to develop a profile of the developmental, health, socio-economic, racial and demographic factors associated with risk, protective and resilience factors that contribute to juvenile delinquency in Aboriginal and Torres Strait Islander Children.

JUVENILE DELINQUENCY

Conducted by Anna Ferrante

Anna Ferrante is an Associate Professor at the Centre for Data Linkage, Curtin University, formerly a Research Associate Professor at the Crime Research Centre, University of Western Australia. As part of the Developmental Pathways Project, Anna is undertaking a population-based study of the dimensions and development of delinquency in Western Australian children. The aim of the project is to contribute to a better understanding of the dimensions of juvenile delinquency and of the impact of various factors on the development of delinquency over the life-course. By exploring the interactions between risk factors and their effect on offending, it may be possible to map 'pathways' from early childhood to juvenile delinquency and later criminal behaviour.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Conducted by Dr Desiree Silva

Dr Desiree Silva is a paediatrician, and Professor of Paediatric Medicine at Joondalup Health Campus and UWA. Due to the escalation of mental health issues in children, Desiree commenced a PhD through UWA and the Telethon Institute for Child Health Research on the risk factors and outcomes of children

and adolescents diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) in Western Australia. Her PhD project uses longitudinal population data provided through the Developmental Pathways Project. This administrative data, along with questionnaire data, is being used to: identify potential antenatal and early neonatal risk factors associated with children requiring treatment with stimulant medication; explore hospital and emergency morbidity, accident related hospitalisation risk, criminal and antisocial behaviour, and service needs associated with children on stimulant treatment for ADHD; examine education outcomes of children diagnosed with ADHD and their level of stimulant medication treatment; and explore the mental health burden of parents and family functioning of children diagnosed and treated with pharmacotherapy for ADHD in WA.

MENTAL HEALTH

Conducted by Janice Wong

Janice Wong is completing her doctorate on the Developmental Pathways Project. Her project is titled 'The relationship between educational and mental health outcomes for Western Australian children: A longitudinal population study'. Using linked longitudinal population data provided through the DPP this subproject seeks to explore the dynamic relationship between children's educational outcomes and their mental health, whilst taking into account variables that have been shown to impact on this relationship. Children who are vulnerable to mental health problems are subsequently at risk of experiencing interference with development, and more specifically, with schooling, and the development of their identity. Results of this study will potentially inform the development of suitable interventions, ultimately with the aim to decrease the prevalence of mental health issues and improve educational outcomes.

The Developmental Pathways Project also facilitates the provision of de-identified non-health linked population level data to a number of other research projects conducted within other research institutions, including those led by Prof Jablensky (Pathways of Risk from Conception to Disease: A Population-Based Study of the Offspring of Women with Bipolar Disorder and Schizophrenia); Assoc Prof Tony Butler (Does Traumatic Brain Injury (TBI) lead to offending behaviour?); and Dr Colleen O'Leary (Investigating the effect of a maternal alcohol-related diagnosis on the educational, juvenile justice, and child protection outcomes of their children and Examining the effect of the dose, pattern, and timing of prenatal alcohol exposure on educational outcomes).

Human Capability

EARLY VOCABULARY DEVELOPMENT: THE IMPORTANCE OF JOINT ATTENTION AND PARENT-CHILD BOOK READING

Brad Farrant, Steve Zubrick.

In this study we brought a bioecological approach to children's early vocabulary development using data for 2,188 children (1,119 male) from the Longitudinal Study of Australian Children. These children had a median age of 9 months (M = 9.3 months, SD = 2.1 months) at Wave 1 and a median age of 34 months (M = 34.2 months, SD = 2.5 months) at Wave 2. We found that the effects of individual (e.g., parent) and environmental (context) characteristics on children's vocabulary development are primarily indirect, mediated through their impact on the proximal processes of joint attention and parent-child book reading. Thus, the findings of our study add to the growing evidence that joint attention and parent-child book reading are important facilitators of children's early vocabulary development.

Funders of the project: NHMRC Program Grant #572742 (BF)

EMPATHY, PERSPECTIVE TAKING, AND PROSOCIAL BEHAVIOUR: THE IMPORTANCE OF PARENTING PRACTICES

Brad Farrant, Tara Devine, Murray Maybery, Janet Fletcher

It has long been argued that empathy for others' plight and the associated altruistic behaviour are key facilitators of social life. Social scientists emphasise the important role that parents play in the socialisation of empathy and prosocial behaviour and research has found that positive parenting practices are associated with higher levels of child prosocial behaviour. In this study we investigated the hypothesis that more empathic mothers are more likely to encourage their child to take the perspective of others and that this is associated with increased child empathy and prosocial behaviour. Participants were 72 typically developing children (66 Caucasian, 6 Asian) aged between 47 and 76 months (M = 61.5 months, SD = 8.3 months). Results supported the hypothesis. Thus, the role played by parents in the development of prosocial behaviour extends beyond warm/sensitive/responsive parenting in infancy. Together these forms of parenting are key factors that facilitate the development of prosocial behaviour.

Funders of the project: University of Western Australia Hackett postgraduate scholarship (BF), University of Western Australia completion scholarship (BF) NHMRC Program Grant #572742 (BF).

GETTING OUR STORY RIGHT

David Lawrence, Francis Mitrou, Daniel Christensen, Glenn Pearson

The Getting Our Story Right project is a collaboration between the Telethon Institute for Child Health Research, the Australian Bureau of Statistics (ABS) and The Department of Health WA (DoHWA) and aims to explore and develop different methods for deriving Indigenous status from multiple data sources using the WA Data Linkage System and examine the impact of these methods on a sample of health and educational outcomes

among the Indigenous population.

Various methods of deriving consistent Indigenous status from a linked data source will be explored and the impact of these methods examined against a selection of health and educational outcomes such as mortality rates, hospitalisation rates, and school-based reading and writing scores from standardised tests.

The overall aim of the project is to produce a set of recommendations for agencies and researchers responsible for the provision of Aboriginal and Torres Strait Islander Statistics, particularly with reference to COAG 'Closing the Gap' indicators. It is envisaged that these recommendations will help agencies and researchers produce consistent, reproducible and meaningful statistics in order to assess the health and wellbeing of Aboriginal people.

Funders of the project: COAG, ARC Discovery Grant DP0877513

SUGAR SWEETENED BEVERAGE CONSUMPTION BY AUSTRALIAN CHILDREN: IMPLICATIONS FOR PUBLIC HEALTH STRATEGY

Katherine Hafekost, Francis Mitrou, David Lawrence and Stephen R Zubrick

Consumption of sugar sweetened beverages 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

PLAYGROUP PARTICIPATION AND THE ASSOCIATED OUTCOMES FOR CHILDREN AND MOTHERS

Kirsten Hancock, David Lawrence, Francis Mitrou, Stephen Zubrick

with David Zarb , Jan Nicholson and Donna Berthelsen

Though thousands of parents and children attend playgroups each week, there is little evidence around the extent to which playgroups achieve their objectives of enhancing child development, supporting parents and encouraging community participation. Using data from around 5,000 families participating in *Growing Up in Australia: The Longitudinal Study of Australian Children*, we found that children from disadvantaged families were less likely to access playgroups than other children, yet these were the children who benefitted most from attending. Children from disadvantaged families scored higher on measures of learning competence and social-emotional functioning at age 4-5 years if they persistently attended playgroup when aged 0-1 and 2-3 years compared to children from disadvantaged families who did not attend.

In a second phase of research, we found that mothers of 4-5 year old children who persistently attended playgroup were more likely to have consistently good support from friends, or to have improved support from friends compared to mothers whose children did not attend, suggesting that socially isolated parents may find playgroups a useful resource to build their social networks.

Finally, we found that compared to children who never attended playgroup, children who did attend playgroups tended to have more books in the home, attended more activities outside the home (e.g. swimming pools, museums, movies), lived in safer neighbourhoods, lived in places with good access to basic services and were more likely to use other child services, like a maternal child health nurse.

Funders of the project: NHMRC program grant #572742

HOW MULTIPLE GENERATIONS OF MENTAL HEALTH PROBLEMS IN FAMILIES INFLUENCES THE WELLBEING OF CHILDREN

Kirsten Hancock, Francis Mitrou, David Lawrence and Stephen Zubrick with Megan Shipley

Research has consistently shown that children of parents with mental health problems are at greater risk of also developing mental health problems. Yet there is limited research around how these mental health relationships evolve over multiple generations, beyond the initial parent-child relationship. In this study, we used data collected from 4,600 families participating in *Growing Up in Australia: The Longitudinal Study of Australian Children* to examine the mental health relationships across three generations of Australian families.

Our results show that the mental health of grandparents matters for children, even in the absence of problems in the parent generation. Compared to children with no family history of mental health problems, the risk of social and emotional wellbeing problems in 4-5 and 8-9 year old children was 1.3 times (95% CI 1.07-1.64) higher for children who had a grandparent, but not a parent, with a history of mental health problems; 3.2 times higher (95% CI 2.3-4.5) for children with only a parent with a mental health problem and 2.6 times higher (95% CI 1.9 – 3.5) for children who had both a parent and a

grandparent with a history of mental health problems.

In our next phase of work we are examining how multiple generations of joblessness and divorce impact upon a range of outcomes for children.

Funders of the project: NHMRC program grant #572742

MEASURING AND MODELLING THE CHILDHOOD DETERMINANTS OF HUMAN CAPITAL FORMATION AND HUMAN CAPABILITY EXPANSION

Stephen Zubrick, Sven Silburn, Dennis Trewin, Ann Sanson, Bill Louden, David Lawrence.

This study uses archival data sources and data linkage capacities to focus on the measurement of human capability across the life course. Specifically the study aimed to integrate archival data with population data registers in the health, education and social services sectors to study patterns of participation (or non-participation) associated with specific education, health and developmental burdens; and to use national data sources such as the Longitudinal Study of Australian Children to compare and validate findings across settings. This study seeks to document the relationship of human capital growth to educational attainment, employment and occupational skill level across the lifespan and how this relates to human capability expansion. The study also sought to inform population health interventions and health promotion through a lifecourse approach to informing the evidence base for these interventions. Key research findings from the study include:

- teenage pregnancy was found to be significantly associated with family type, highest school year completed by primary carer, combined carer income, whether the primary carer was a smoker and whether the girl displayed aggressive and delinquent behaviours during childhood and adolescence. Aggressive and delinquent behaviours were predictive of teen pregnancy even when observed at young ages.
- deliberate self-harm was found to be significantly associated with female sex, primary carer being a smoker, being in a step or blended family, having more emotional or behavioural problems than other children, living in a family with inconsistent parenting style, and having a teenage mother.
- people with common mental disorders such as anxiety or depression smoke at substantially higher rates than the remainder of the community, and represent about one-third of Adult smokers in Australia. People with these disorders are more likely to start smoking, less likely to quit, and smoke on average for longer duration, despite wanting to quit and trying to quit as much as anyone else. Mainstream anti-smoking campaigns that have been successful in the broader population have had lesser success for people with mental health problems.
- Investigation of data on food production and food imports into Australia has identified that sugars in processed manufactured foods imported into Australia are not included in estimates of sugar consumption. This is traditionally estimated from the size of the sugar crop minus sugar exports. As importation of manufactured foods with high sugar content has increased dramatically over the last 15 years, this may have downplayed the role of sugar consumption in the increasing rate of obesity and metabolic diseases.

Funders of the project: COAG, ARC Discovery Grant DP0877513.

CHILD AND ADOLESCENT COMPONENT OF THE NATIONAL SURVEY OF MENTAL HEALTH AND WELLBEING

Jennifer Hafekost, David Lawrence, Stephen Zubrick

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, and the Institute is participating in sample design and content development work in preparation for a second national survey of children and young people.

The broad aims of the National Survey of Mental Health and Wellbeing initiative have been to determine how many Australians have which mental disorders, what is the impact of these disorders (on individuals, families and communities), and what services are being used by people with mental disorders.

The development work for this study included reviewing surveys of child and adolescent mental health and wellbeing internationally, reviewing relevant instruments and questionnaires in the field, and facilitating consultation with relevant stakeholders to help refine and articulate the goals for the survey. Methodological work to develop an appropriate sampling strategy to achieve these goals was undertaken. The work also identified emerging content areas relevant to the social and emotional wellbeing of children and young people including the impact of new and emerging technologies on peer relations and bullying behaviours, and the role of social inclusion in fostering emotional wellbeing.

Funders of the project: Australian Government Department of Health and Ageing

EARLY LIFE INFLUENCES ON CHILD AND ADOLESCENT MENTAL HEALTH PROBLEMS: A LIFE-COURSE APPROACH TO PREVENTION AND INTERVENTION

Dr Monique Robinson (Supervisor: W/ Professor Stephen R Zubrick)

My current work explores the early life influences on mental health development in order to inform both prevention and

intervention. 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. My research exists within this new paradigm, exploring the early life influences on behavioral development. I continue to research numerous novel risk factors present in the prenatal period that are linked to an increased risk for mental health problems throughout childhood, including stress, maternal obesity, preterm birth, cigarette smoking, alcohol consumption, low levels of Vitamin D and hypertension. I am also actively involved in collaborations with Columbia University (USA), McMaster University (Canada), the Murdoch Children's Research Institute (Melbourne) and the School of Population Health (Perth) on various projects looking at psychological outcomes following adverse early life exposures.

Funders of the project: Australian Rotary Health Colin Dodds Postdoctoral Research Fellowship

AUSTRALIAN EARLY DEVELOPMENT INDEX

Sally Brinkman, Stephen Zubrick, Tess Gregory and Louisa Santucci

The Australian Early Development Index (AEDI) is a population measure of young children's development. Like a census, it involves collecting information to help create a snapshot of children's development in communities across Australia. Teachers complete the checklist for children in their first year of full-time schooling. The AEDI measures five developmental domains:

- Physical health and wellbeing
- Social competence
- Emotional maturity
- Language and cognitive skills (school-based)
- Communication skills and general knowledge

The AEDI is based on the Canadian Early Development Instrument (EDI) which was developed by Dr Janus and Dr Offord at the Offord Centre for Child Studies, Mc Master University. In Australia, the Canadian EDI checklist was first trialed in the northern metropolitan suburbs of Perth in 2002 and 2003, with around 4,300 children. Since 2004 the adaption of the EDI - now called the Australian EDI, or AEDI has been carried out by the Centre for Community Child Health in partnership with the Telethon Institute for Child Health Research.

In 2009, the AEDI was completed nationwide for the first time with the Australian Government providing $21.9 million for the implementation of the AEDI in recognition of the need for all communities to have information about early childhood development. Between 1 May and 31 July, information was collected on 261,203 children (97.5 per cent of the estimated national five-year-old population). The initial results provide a snapshot of the early childhood development outcomes for children in communities across Australia. The government has now taken ownership of the AEDI National Program and has committed to undertake an AEDI Census of child development once every three years. Thus, in 2012, the AEDI will be completed nationwide for a second time. Data will be collected between May and July 2012, with results made public in early 2013. This second round of data collection will provide the first opportunity to explore change in the level of developmental vulnerability for children living in different communities, states and territories within Australia.

In 2011, the Australian Government Department of Education, Employment and Workplace Relations (DEEWR) awarded $1.5 million in funding directly to TICHR to explore the 2009 and 2012 AEDI data and deliver on policy focused research. The research will focus on a range of questions pertinent to early childhood development such as:-

- Are there jurisdictional differences in the level of developmental vulnerability across Australia?
- Is there a differential impact of living in mining towns vs. non-mining towns for Aboriginal child development?
- How does the AEDI predict later outcomes during the primary school years?

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 Childrens Research Institute, and the Telethon Institute for Child Health Research, Perth, to deliver the AEDI.

Early Child Development, Program Evaluation:

RANDOMISED CLUSTER CONTROL TRIAL EVALUATING THE IMPACT OF AN EARLY CHILDHOOD EDUCATION AND DEVELOPMENT INITIATIVE ACROSS INDONESIA

Sally Brinkman, Menno Pradhan, Amanda Beatty, Amelia Maika, Elan Satriawan

With a greater scale for improvement in school readiness outcomes, the evaluation of ECED programs in the developing countries affords a greater scope for investigation into the facilitators and barriers for success. This ECED program that we are evaluating represents a significant investment on behalf of the Republic of Indonesia and the World Bank.

With significant economic growth over the last 5 years, Indonesia is currently classified as a lower to middle income country. Despite this fact, there are over 35 million people living below the poverty line – representing 16% of the population. In addition it is estimated that up to half the population are vulnerable to poverty with the inequality between rich and poor vast. A large disparity in socio-economics, nutrition, education and health exist between districts, with infant and child mortality rates significantly higher in the poorer communities. In addition, children from the poorer villages start school later, complete fewer years of schooling and have higher drop out and repetition rates.

The objective of the Early Childhood Education and Development program is to improve poor children's overall development and readiness for further education by (i) increasing the delivery of ECED services in targeted poor communities using a community-driven approach and (ii) developing a sustainable system for delivering ECED services. The project will reach approximately 738,000 children aged 0 to 6 and their parents/ caretakers living in about 6,000 poor communities (dusuns) located in 3,000 villages within 50 districts. Participating districts have been selected according to poverty level and their commitment to developing ECED services.

The outcomes of the research will enable us: to determine (if and to) what extent the ECED project improved children's development, attendance and readiness for school; to what extent the ECED project improved parental awareness and practices; if the project increased the availability and utilisation of ECED services and if so, how those impacts differed by gender, wealth, and level of service delivery at baseline. It is essential that the research will be able to determine what factors contributed to any success or failures by the ECED program. By including local academics in the research we will facilitate cultural relevance, local knowledge and contextual relevance to the research (instrument development, fieldwork nuances through to identification of key stakeholders etc). A well designed and implemented impact evaluation will provide a unique opportunity to inform the current and future practices in Indonesia and abroad. In addition the evaluation will utilize outcome instrumentation that can be internationally referenced and thus rigorous piloting and cultural adaptation of internationally recognized instruments will be required.

The AisAID ADRA Grant has enabled the employment of two early career academics based at the University of Gadja Mada (UGM) in Indonesia. As both academics are teaching university students, building their capacity, skills and knowledge will not only benefit themselves but their current and future students. There is a clear and recognised deficit in Indonesia in the knowledge and capacity regarding high quality research methods, research application, instrument development, statistical/analytical skills and the importance of good quality evaluations of programs (such as this ECED program) as well as simply a lack of understanding of the importance of early child development and education. Building local capacity will decrease the current reliance on "fly-in consultants". Over the time of this research our aim is to ensure that Dr Elan Satriawan and Ms Amelia Malika will independently have the skills, knowledge and confidence to be able to design, undertake and manage such large scale research programs and have the confidence to disseminate the research findings to government, donors and other stakeholders including within the academic literature.

Funder of the project: Australian Development Research Award (ADRA) awarded by AusAID

INTERNATIONAL CONSORTIUM FOR THE MONITORING OF CHILD DEVELOPMENT

Magdalena Janus, Sally Brinkman, Clyde Hertzman, Mary Young

As international interest and acknowledgment grows around the importance of monitoring child development various countries are looking for support in initiating monitoring activities. As such an International Consortium for the Monitoring of Child Development has been formed between the Offord Centre at McMaster University and the Human Early Learning Partnership in Canada along with the Telethon Institute for Child Health Research and the Centre for Community Child Health in Australia, with the WorldBank as a partner organisation. Currently we are involved in supporting Indonesia, Peru, Ireland, the United Arab Emirates, Chile and Brazil in their endeavors to adapt the EDI.

Funders of the project: Supported by: WorldBank, Van Leer Foundation and UNICEF.

FIVE-UP STUDY (NSW)

Vaughan Carr, Kristin Laurens, Rhoshel Lenroot, Patricia Michie, Allyson Holbrook, Melissa Green, Sally Brinkman, Frini Karayanidis, Miles Bore, Helen Stain, Carmel Loughland, John Attia, Stephen Lynn, Max Smith, Richard Matthews, Michael Tarren-Sweeney, David McKie, Felicity Harris

A healthy start to life is one of Australia's key goals and primary research priorities. Where at all possible, prevention and early intervention are deemed to be of critical importance. This calls for longitudinal data collection to improve the knowledge base for identifying children at risk of adverse mental health and social outcomes in childhood, adolescence, and early adulthood. Research has shown that 75% of mental disorders commence before the age of 25 years, and that 46% of adults report the occurrence of at least one psychiatric disorder over their lifetime (with 25% reporting a current psychiatric disorder).

The NSW Child Development Study is being designed as a 15-20 year project to identify potential health-related vulnerability and protective factors in children, and to examine their relationships to a variety of health, wellbeing and social outcomes in adolescence and young adulthood. Improved knowledge of these factors will enable the identification of children at risk of a variety of negative health, wellbeing and social outcomes, and may lead to the development of effective early intervention and prevention programs.

The main outcomes of interest are in the following domains.

- Mental health (e.g., early onset severe mental illnesses, drug and alcohol abuse)
- Health (e.g., early onset chronic diseases)
- Education (e.g., academic achievement, failure to complete high school education)
- Welfare (e.g., DoCS notifications and interventions)
- Workforce (e.g., unemployment)
- Criminal offending (e.g., arrests, charges,

court outcomes, imprisonment)

Using a NSW population cohort, this project aims to identify vulnerability and resilience factors, emerging from birth to 10 years of age, that relate to developmental functioning (social, emotional, behavioural, physical and cognitive functioning) and school achievement. The research has two key components: 1) a comprehensive inter-agency record linkage; and 2) a cross-sectional child and parent assessment. Record linkage is being conducted under the auspices of the Centre for Health Record Linkage (CheReL), in which the use of probabilistic record linkage techniques help to ensure strict privacy protocols are adhered to.

To supplement the information available through record linkage, the research includes a cross-sectional child and parent assessment to be administered to the cohort in 2014 (during Grade 5). This assessment will be developed and administered in partnership with the NSW Department of Education, and in collaboration with educational experts and other stakeholders (e.g., teachers unions).

There will be significant opportunities for partnership and collaboration for TICHR researchers as such linked databases build across the country.

Funders of the project: Australian Research Council, NSW Department of Health, NSW Department of Education and Community Services.

LOOKING AT LANGUAGE

Mabel Rice, Cate Taylor, Stephen Zubrick, Shelley Smith

A child's ability to communicate is one of their most important developmental accomplishments and builds the foundation for success at school and beyond. LOOKING at Language is a population based longitudinal study of individual differences in language development from infancy through adolescence. The study is an international collaboration between Professor Mabel Rice from the University of Kansas, Professor Cate Taylor and Winthrop Professor Stephen Zubrick from the Telethon Institute for Child Health Research and the University of Western Australia and Professor Shelley Smith from the University of Nebraska Medical Center.

Data collection for this project is based entirely in WA and involves 1000 families, 800 are families with twins. We established that 13% of single-born children are late to start to talk at 24 months and that one in five of these children is at risk for language impairment at 7 years. We are currently writing a paper on the prevalence of late language emergence in twins. We are set to realize the publication opportunities from this study over the next few years when data from successive birth cohorts is available from each wave of follow-up (i.e., 2, 4, 6 and 9 years). The study provides a unique multidimensional population based longitudinal dataset for studying the many factors that influence language development and reading from infancy to adolescence.

Funders of the project: USA National Institutes of Health

THE WESTERN AUSTRALIAN PREGNANCY COHORT (RAINE) STUDY – NOT COMPLETE

The Raine Study began in 1989 at King Edward Memorial Hospital with the recruitment of 2900 pregnant women in early pregnancy. These families were followed through pregnancy and child birth, and 2868 families were recruited for long term follow to study the origins of health and disease. After birth, The Raine cohort participants been reviewed in detail on ten occasions at ages 1, 2, 3, 5, 8, 10, 14, 17, 18 and during 2011 at 21 years of age. This cohort review has been conducted at the Lions Eyes Institute by the TICHR Raine Study Team, ophthalmologists and orthoptists from LEI and UWA medical students.

The Raine Study is one of the largest successful prospective cohorts of pregnancy, childhood and adolescence in the world. 80% of the original participants are still active and committed to the project. The Raine cohort demographics are representative of the wider Western Australian population. Each member of the cohort has over 85,000 measures of health and disease and information on more than 2.5 million genetic variants. The Raine Study is a unique resource for WA, Australian and International researchers.

The Raine Study is governed by the Raine Study Executive Committee and managed by Raine Study Manager and Scientific Director. There are 24 research groups utilizing the Raine Study Cohort data and there is growing collaborative research between Raine Study Principal Investigators. National and international collaborations with the Raine Study are continuing to develop and add value to the cohort and expand research opportunities. 2011 saw the cohort members participate in the 20/21 year cohort follow up at LEI consisting of comprehensive eye testing, a DEXA scan, a fibroscan, follow up of longitudinally collected anthropomorphic measures (height, weight, body measurements), blood pressure and questionnaire data. Male cohort members also participated in the Male Fertility Study which was conducted separately to the Eye Health Study.

In February 2011 the Raine Study PhD top-up scholarships were awarded to Nicole Warrington and Lauren Hollier.

On Sunday 6th November 2011, the Raine Study organized a public exhibition event at the Government House Gardens in Perth as a celebration and exhibition of the 21 years of research in the Raine Study. Raine Study participants and their families were invited, as well as the Raine Study Research Community. The Event was a celebration of the commitment and amazing dedication of the Raine Study Cohort participants over the past 21 years. On display were the achievements of the Raine Study over the past 21 years. Exhibition stands were created by some the 24 Raine Research Groups displaying their research and findings.

The Governor of Western Australia, His Excellency, Mr Malcolm McCusker AO QC and Mrs Tonya McCusker, joint patrons of the Raine Study, formally opened the event. His Excellency

presented awards to Professor John Newnham for outstanding contribution to Science, and to Professor Leon Straker, Professor Peter O'Sullivan and Dr Anne Smith for outstanding contribution to public health. Professor Fiona Stanley presented awards to some of the Raine Study Participants who had made a substantial effort in participating in the Raine Study. The day was an outstanding success.

The Raine Study Annual Scientific day was held at UWA Club on 18 November 2011. This was an extremely successful meeting with posters and presentations from over 20 Raine Study Researchers. The Raine Medical Research Foundation prize for best poster was awarded to Dr Monique Robinson and the Raine Medical Research Foundation prize for best presentation was awarded to Ms Carly Herbison.

In November 2011, the Raine Study was successful in being awarded six NHMRC funded Grants. Planning was started for the 23 year follow up of the cohort examining sleeping disorders and asthma in young adults.

Successful Grant Applications - Raine Study

1021105, Prof D Mackey et al, MRC Genome-wide association study (GWAS) for juvenile-onset myopia and its component measures to identify molecular pathways to prevent myopia

1021858, Prof G Hall et al, Transition from childhood to adult asthma: Predicting persistent and adult-onset asthma in young adults in the Raine longitudinal birth cohort

1027449, Prof P Eastwood, The evolution of childhood obesity and its relationship to adult sleep disordered breathing

1022134, Prof W Oddy et al, Nutritional determinants of cardio metabolic risk and mental health: from infancy to adulthood

1030148, Profs D Hunt, D Mackey, Myopia and colour vision: potential impact of colour vision gene variation on susceptibility to myopia

1037966, Prof W Oddy et al, 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.

In 2011, there were 47 Raine Study publications in peer reviewed journals.

Raine Study Research Groups

1. Anaesthesia
2. Asthma & Allergy
3. Cardiovascular & Metabolic
4. Cognitive Neuroscience
5. Dental Health
6. Developmental Origins of Health and Disease
7. Eating Disorders
8. Endocrinology
9. Epigenetics
10. Gastrointestinal & Heptology
11. Genetic Epidemiology
12. Growth & Nutrition
13. Hypothalamic-Pituitary-Axis
14. Infectious Disease
15. Language Development
16. Mental Health
17. Musculoskeletal
18. Ophthalmology
19. Otolaryngology
20. Physical Activity
21. Pregnancy & Birth
22. Reproductive Health
23. Risk Taking Behaviour
24. Sleep

Core Management funding:

- The Telethon Institute for Child Health Research
- The University of Western Australia
- Raine Medical Research Foundation, UWA
- UWA Faculty of Medicine, Dentistry and Health Sciences
- Women and Infants Research Foundation
- Curtin University
- Research Funding
- National Health and Medical Research Council of Australia
- National Hearth Foundation
- Rotary Health Research
- Canadian Institute of Health Research

Scientific Director: Associate Professor Craig Pennell

Study Manager: Ms Jenny Mountain

Data Managers Dr Louise Mckenzie, Ms Angela Jacques

Team Leader: Ms Diane Wood

Raine Study Team 2011

Jenny Mountain, Louise McKenzie, Angela Jacques, Diane Wood, Alex Baptista, Emilly Hockley, Natasha Larter, Jessica Hall, Annegret Harries, Sue Greene (phlebotomist), Denny Craig, Carolyn Smargiassi, Amy Smithies

THE RAINE STUDY 20 YEAR FOLLOW UP - THE RAINE EYE HEALTH STUDY: AN OPHTHALMIC FOLLOW-UP STUDY OF A LONGITUDINAL BIRTH COHORT AT AGE 20/21 YEARS

David Mackey, Alex Hewitt, Alla Soloshenko, Sandra Oates, Seyan Yazar, Alex Tan, Hannah Forward, Charlotte McKnight, Craig Pennell, Jenny Mountain, Raine Study Team

The Raine Study commenced the 20 to 21 year follow up of the cohort participants in 2010 carried on in 2011. The Raine Eye Health Study is examining eye health in an age group for which very little data exist. It is presumed that young adults have the best vision and thus very few people have studied people of this age group. The primary aims of this study are: (1) To document the prevalence of the

eye conditions: refractive error, amblyopia and strabismus, in young adults; (2) To determine the population distribution of endophenotypes/ biometry related to eye diseases in young adults; (3) To determine genetic and early environmental factors that influence ocular biometry and predispose to ophthalmic disease; and (4) To investigate the interaction of early life, familial, lifestyle, demographic and genetic risk factors with these conditions, and their endophenotypes. Raine Study participants are invited to the Lions Eye Institute to undergo a comprehensive set of eye tests checking eye sight and vision and the health of the eyes. The results of all these tests are given to the participant during the follow-up, and where necessary glasses prescriptions or treatment are provided. In addition participants complete a questionnaire which includes information on sociodemographics, relationships, mental health, spinal pain, physical activity, asthma and atopy, risk taking behaviour and medical history, and the Cancer Council short food frequency questionnaire. Participants also have physical measurements (height, weight, anthropometry) and blood pressure testing.

During the assessment the participants have a DEXA scan, which measures body composition (fat mass, lean mass and bone density). Participants also provide a fasting blood sample at a domiciliary visit by the Raine Phlebotomist.

Funders of the project: NH&MRC 634445, 634457, 634509, 1003424, CIHR_MOP-82893, Raine Core Management Funding Australian Foundation for the Prevention of Blindness, Lions Eye Institute, Alcon Research Institute

THE RAINE STUDY 20 YEAR FOLLOW UP - DEXA SCAN IN THE RAINE COHORT

Craig Pennell, Leon Straker, Raine Study Team

Bone mineral content, body composition and percentage body fat are assessed from dual energy X-ray absorptiometry (DEXA) scans. During the 20 year follow up visit, each Raine participant has a whole body DEXA scan using a Norland XR36 Quickscan machine. DEXA is the most widely used clinical tool for the assessment of skeletal integrity owing to its efficiency, precision and accuracy. The DEXA provides measures of body composition (lean mass, fat mass, bone mass) as well as bone density. The DEXA is considered the 'gold' standard measurement of adiposity.

Funders of the project: Canadian Institute of Health Research CIHR (Lye et al, MOP-82893)

THE RAINE STUDY 20 YEAR FOLLOW UP - FIBROSCAN IN THE RAINE COHORT

Eng Gan, Leon Adams, John Olynyk, Oyekoya Ayonrinde, Raine Study Team

The prevalence of Non-alcoholic fatty liver disease (NAFLD) in the Raine cohort at 17 years was 13 %, placing these subjects at possible risk of further complications. The major determinant of severity and outcome for NAFLD is the degree of hepatic fibrosis (tissue scarring in the liver). Assessment of fibrosis has traditionally required the use of a liver biopsy. However, due to its invasive nature and problems of sampling error, variability in interpretation and cost, non-invasive alternatives such as Fibroscan® (Echosens™, France) have recently been developed. A FibroScan fulfils many criteria required for non-invasive assessment of liver fibrosis. It is quick; taking on average five minutes, has good reproducibility, is most importantly, acceptable to the patient, and examines a relatively large sample of the liver. As part of the 20 year follow up, Fibroscan® is being used in the Raine cohort to non-invasively quantify hepatic fibrosis in the Raine cohort and establish norms in this age group.

Funders of the project: NH&MRC 634445

RAINE STUDY 20 YEAR FOLLOW UP - THE EARLY LIFE ORIGINS OF IMPAIRED TESTICULAR FUNCTION

Roger Hart, Stephen Junk, Dorota Doherty, Michelle Pedretti, Raine Study Team

Over the last few years there have been reports that male sperm counts are diminishing and that this is beginning to be obvious at a younger age. Many of these findings are based on sperm counts from people seeking infertility treatment, and not from healthy groups of people. It is not known why some people have low sperm counts. It may be through exposure to passive smoking, or early life events. Obesity is one of the factors that lead to a reduced sperm count, and it is believed that there might be other possible contributors in childhood health and diet. As a population we are being exposed to increasing amounts of chemicals in the environment (endocrine disrupters) which may have an effect. This study of male participants in the Raine Study cohort is the first study to utilise a large and well-established cohort prospectively followed from intrauterine life through adolescence into adulthood to investigate key fetal and childhood events leading to reduced semen parameters and decreased testicular volume. Recruitment began in April 2010 and continued through 2011. Results and clinical support if necessary, are provided to participants.

Funders of the project: NH&MRC 634457.

RAINE STUDY 20 YEAR FOLLOW UP – EARLY INFLUENCES ON ADULT BEHAVIOUR AND THINKING STYLES

Andrew Whitehouse, Martha Hickey, Raine Study Team

This study is examining autism-like behaviours in the general population to test the two most prominent biological theories of Autism Spectrum Disorders (ASDs), namely, that ASDs are caused by (1) early brain overgrowth, or (2) exposure to elevated levels of fetal testosterone. There is agreement that autism-like symptoms, including social and communication difficulties, are on a continuum in the general population, with Autism Spectrum Disorder (ASD) representing the extreme end of the distribution. This study examines autism-like behaviours in the general population by requesting the Raine Study Cohort to complete a 50-item questionnaire measuring systematic (logical and organised) and empathetic (understanding and sympathetic) patterns of thinking. Raine Study participants are given the opportunity to either log onto the Raine

Study Website with a unique identifier and password and complete the questionnaire online or to complete a paper copy. Measures of head circumference and fetal testosterone are available on the cohort from prenatal ultrasounds and cord blood.

Funders of the project: Research Funds from Prof Martha Hickey

RAINE STUDY: RISK TAKING BEHAVIOUR GROUP

CHILDHOOD DETERMINANTS OF RISKY SEXUAL BEHAVIOUR IN ADOLESCENCE: A PROSPECTIVE COHORT STUDY

Rachel Skinner, Martha Hickey, Eugen Mattes, Dorota Doherty, Anthony Smith, Susan Rosenthal, Spring Cooper, Michael Smith

This research project aims to identify childhood factors which influence an adolescents' likelihood to initiate sexual activity at a young age, and engage in sexual risk taking. Risky sexual behaviour contributes to unplanned teenage pregnancy, sexually transmitted infections (STIs) and adverse social, emotional and physical health outcomes in adolescence into adulthood. We have little understanding of early determinants of risky sexual behaviour.

The Raine Study provided extensive biological, psychological, psychosocial, family, individual and environmental characteristics collected at all ages. This unique dataset is currently being utilised to undertake a world first analysis of causal pathways through early life to sexual risk-taking in adolescence.

Initial analyses show higher scores for Total Behaviour Problems and the Externalizing Behaviour subscale of the Child Behaviour Checklist (CBCL) in participants who had already engaged in sexual intercourse compared to those who did not. In addition, participants who were identified with clinically recognized delinquent and aggressive behavioural problems at ages 5, 8, 10 and 13, were more likely to have engaged in sexual intercourse. These unique data indicating early predictors of risky sexual behaviour in adolescence may help determine how and at what ages interventions may be effective.

Funders of the project: NH&MRC 634509

FRUCTOSE INTAKE AND FOOD SOURCES IN WEST AUSTRALIAN ADOLESCENTS

Therese O'Sullivan, Wendy Oddy, Jill Sherriff, Susan Woolley

Fructose is widely distributed within the Australian food supply; however data on fructose intakes is limited, particularly in children and adolescents. Excessive fructose consumption may have implications for dyslipidemia, fatty liver disease and obesity. This research aimed to quantify fructose consumption and identify major food sources of fructose, in adolescents participating in the 14 year follow-up of the Western Australian Pregnancy Cohort (Raine) Study. Dietary intake was assessed by 3-day food records and entered in the FoodWorks dietary analysis program. Total fructose values for individual foods were linked from the Nutrient Tables for use in Australia, the University of Minnesota Nutrition Coordinating Centre Food and Nutrient Database and the Canadian Nutrient File. We found that fructose contributed 9.1% of total energy intake for the group. Boys reported higher absolute fructose intakes than girls (58.9 g ± 26.6 g vs 48.3 g ± 20.1 g, respectively, $p<0.001$), while girls had higher energy adjusted fructose intakes than boys (55.7 g ± 16.1 g vs 51.8 g ± 20.2 g, respectively, $p=0.002$). Major food sources of fructose in the Raine cohort were beverages, in particular soft drinks, followed by fruit and confectionery. No significant associations were found between fructose intake and level of physical activity, BMI or socio-economic status indicators in unadjusted analyses, however adolescents from higher socio-economic groups consumed more fructose from fruit whereas adolescents from lower socio-economic groups consumed more fructose from beverages. To our knowledge, this is the first study to describe fructose intake and food sources in Australian adolescents. Our results are similar to those previously reported in studies of US adolescents.

Funders of the project: NH&MRC Program Grant #353514. Heart Foundation/ Beyond Blue Strategic Research Initiative grant

EATING DISORDERS IN WESTERN AUSTRALIA: PREVALENCE, MAINTAINING FACTORS AND PROSPECTIVE RISK FACTORS

Karina Allen, Sue Byrne, Wendy Oddy

This 4-year project commenced in June 2010 and aims to determine the prevalence of eating disorders at two time points in adolescence, in a population-based cohort followed over time; identify factors that predict the persistence of eating disorders across adolescence; and identify prospective risk factors for early and later-onset adolescent eating disorders. The research utilises data from the Western Australian Pregnancy Cohort (Raine) Study. Eating disorder symptoms were assessed at the 14, 17, and 21-year Raine Study follow-ups, and data from the 14 and 17-year follow-ups have now been analysed. The 21-year data will become available for use in 2012.

We found that the prevalence of full and partial eating disorders in the Raine Study cohort increased from 6% at age 14 to 9.5% at age 17. Of the adolescents with an eating disorder at age 14, approximately half continued to report significant eating pathology three years later. These participants also reported significant and persisting problems with depression and anxiety. Fewer than 20% of the Raine Study participants identified as meeting criteria for an eating disorder had been diagnosed with, or treated for, an eating disorder in the community.

Raine Study children who were perceived as overweight by their parents at age 10 years were three times more likely to have developed an eating disorder by age 14 than children who were not perceived as overweight by their parents. Parent-perceived child overweight was a more powerful predictor of eating disorder development

than children's measured weight and height, suggesting that it may be concern and awareness about weight status, rather than overweight status per se, that is associated with eating disorder risk.

Over the last year, we have found that adolescents with an eating disorder report a significantly lower intake of key macro and micronutrients when compared to adolescents without an eating disorder. Adolescents with an eating disorder *and* pronounced depressive symptoms also report a significantly lower intake of fatty acids than adolescents with an eating disorder but no pronounced depression. Low fatty acid intake has been linked to depression previously, and our findings highlight the importance of considering this variable in relation to depressive symptoms in eating disorders.

We have also found that a subset of adolescents with eating disorders experience neurocognitive difficulties, with a tendency to focus on detail at the expense of the bigger, global picture. This neurocognitive style (known as weak central coherence) has been documented in clinical samples of eating disordered participants but this is the first time it has been identified in a community sample.

Our findings have added to the small body of prospective research on risk and maintaining factors for eating disorders. Analysis of the 21-year data will allow us to extend these results further, and the latter stages of the project will focus on translating research outcomes into practical strategies to facilitate effective prevention and early intervention efforts for eating disorders.

Funders of the project: National Health and Medical Research Council (NHMRC)

Social determinants of child health/social epidemiology

PARENTAL WORK HOURS AND QUALITY OF DIET IN ADOLESCENTS

Jianghong Li, Wendy Oddy, Therese O'Sullivan, Sarah Johnson

The study investigates the association of mother's and fathers' work hours and other socioeconomic factors with diet quality in a cohort of adolescents followed from pregnancy to age 13 in Western Australia (the Raine Study), using a diet quality index and dietary patterns developed at the Institute for Child Health Research.

Funders of the project:

Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

This work has now been published in *Public Health Nutrition*

Jianghong Li, Therese O'Sullivan, Sarah Johnson, Fiona Stanley, Wendy Oddy. Maternal work hours in early to middle childhood link to later adolescent diet quality. *Public Health Nutrition* (accepted 25 October 2011: published online first: http://journals.cambridge.org/repo_A84ow7rn).

PARENTAL WORK AND CHILD HEALTH AND DEVELOPMENT

Jianghong Li, Garth Kendall, Lyndall Strazdins, Mike Dockery, Sonia Andrews, Sarah Johnson, Rachel Skinner, Wen-Jui Han (The US).

The project aims to investigate the impact of parental employment status and non-standard work schedules on the health and wellbeing of Australian children/adolescents and to shed new light on the social and economic causes of the high prevalence of mental health problems in today's children. The proposed research will be based on data from Longitudinal Study of Australian Children (LSAC) and the Western Australian Pregnancy Cohort Study (Raine). The project draws on multidisciplinary expertise from sociology, social epidemiology, developmental epidemiology, clinical psychology and labour economy. We have conducted a comprehensive review of the literature on non-standard work schedule and child mental health and behavioural problems and the review will inform specific research aims and questions.

This program of research investigates the following outcomes: Mental health, risk taking behaviours, body mass index, and school achievement.

Funders of the project:

Projects undertaken by Dr Jianghong Li and supported by The Foundation for Children and her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

MATERNAL STRESSFUL EVENTS IN PREGNANCY AND NUMERACY AND LITERACY AT GRADE 5

Jianghong Li, Monique Robinson, Anke van Eekelen, Jonathan Foster, Eva Malacova.

This study examines the timing and number of stressful events in pregnancy and their link with numeracy and literacy achievement in a subset of the Raine Cohort children in grade 5 who attended government schools in WA. The aim of the study is also to demonstrate the importance of examining gender difference in the impact of maternal stressful events in pregnancy on offspring's school achievement and to elucidate the need to distinguish between confounding factors from mediating factors in the causal pathway.

Funders of the project:

Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

This work has resulted in a journal article currently under revision for resubmission to *Journal of Pediatrics* in April 2012.

HIV VULNERABILITY IN OUT-OF-SCHOOL ADOLESCENTS AND YOUTH IN YUNNAN, CHINA

Lijun Yang (China), Jianghong Li.

This is a UNICEF funded project based in China and I am a collaborator on the project. The project aims to understand the level of

knowledge about HIV transmission and prevention and risk taking behaviours in a random sample of out-of-school adolescents in Yunnan Province. Cross-sectional data has been collected and the project is at the stage of analysis.

Funders of the project:

Projects undertaken by Dr Jianghong Li and supported by her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

This work has been accepted for publication in *World Journal of AIDS* (5th April 2012):

Jianghong Li, Lijun Yang, Zhouyang Ren , Chongbin Mo, Dingwen Chen, Fuqiang Dai, Mingzhong Jiang, Zhijie Tang, Peter Jacoby. HIV Vulnerability in out-of school adolescents and youth in Yunnan, China. *World Journal of AIDS* (accepted 5th April 2012).

HOUSING AND CHILDREN'S HEALTH AND DEVELOPMENT

M Dockery, G Kendall, J Li, L Strazdins, F Chan, R Ong, R Seymour, A Mahendran

This is a scoping study that provides a review of international research literature on the link between housing and children's health and development and it proposes a research plan for developing this area of research in Australia. Further funding has been obtained from Australian Housing and Urban Research Institute to carry out the research plan in 2011 and beyond. The project will investigate the effect of housing location and housing quality and ownership on child developmental outcomes.

Funders of the project:

Australian Housing and Urban Research Institute

DETERMINANTS OF CHILD POVERTY IN THE US

Jianghong Li, Joachim Singelmann (the US).

The proposed project will build on the analyses of family poverty in the Mississippi Delta and the Texas Borderland recently carried out by Singelmann and his associates. A key finding of their research has been the importance of poverty-intervention programs that target specific socio-demographic groups. Their results show that the correlates of poverty differ among race and ethnic groups as well as among family types (both parent vs. single parent). The proposed project will extend these analyses to the third high-poverty region in the United States, which is Central Appalachia. All three regions have a poverty rate exceeding 20 %.The focus of the proposed project will be on the determinants of child poverty and differences in these determinants by race, ethnicity and household type. By focusing on the three poverty regions mentioned above, such race/ethnic differentiation will be possible, given the high concentration of blacks in the Delta and of Latinos in the Borderland.

Funders of the project:

Projects undertaken by Dr Jianghong Li and supported by The US Studies Centre at the University of Sydney and her Curtin Research Fellowship, Curtin Health Innovation Research Institute, Centre for Developmental Health, Curtin University.

This project has been completed and a final report submitted to the funder in April 2012.

Childhood Obesity

INVESTIGATING METHODS FOR MANAGING CHILDHOOD OBESITY

Lisa Gibson

Currently there are no satisfactory treatments or prevention strategies for overweight and obese children. New treatment approaches to the management of childhood obesity are needed. This project aims to develop, test and disseminate a new intervention for childhood obesity. The approach is novel in that mothers will be the primary agents of change. There are several compelling reasons for this. Mothers play a critical role in shaping children's eating behaviours, and influence food choice through role modelling. It is likely that changes in the mother's eating and exercise habits will lead to a parallel change in the pre-pubertal child's eating and exercise behaviours.

The intervention program is based on a cognitive behavioural treatment (CBT) for obesity developed at the University of Oxford. The existing CBT has been modified for use with mothers of primary school children. Also, for the purposes of this project, modules focusing on parenting skills, educating parents about eating and exercise behaviours in children and promoting psychosocial wellbeing in children have been added to the original CBT.

Assessment protocols have been developed for the trial of the intervention program. These assessment protocols include self-report questionnaires and semi-structured interviews which will be administered to mothers and children both prior to commencing the intervention program and at completion of the intervention program.

In 2011 we attempted to implement the intervention program in the City of Gosnells to help families manage weight and eating issues. The program (HELP: Healthy Eating and Lifestyle Program) was advertised in a range of different locations (local newspapers, radio, school newsletters etc). Unfortunately, we were not able to attract the number of families we had hoped to participate in the program.

Work has now begun on finding out why families did not respond to the program as we would have hoped. This has involved two components. Firstly, a questionnaire was sent out to all parents of primary school children in the City of Gosnells to obtain feedback on the methods of advertising and the format of the program. Secondly, focus groups were conducted with community health workers from the Gosnells Early Years Action Group (GEYAG). The information gathered from the focus groups and the questionnaire will be

used to help understand why families are not participating in our weight reduction program and also to develop a program that is acceptable to families experiencing eating and weight issues.

Funders of the project: Western Australian Health Promotion Foundation (Healthway)

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Dr Emma Glasson, BPsych, BSc(Hons), PhD

Dr Rebecca Glauert, BPsych(Hons), PhD

Jackie Goldfinch

Jo Granich, BSc MPH

Suzanne Green, REN, Phleb

Andrew Greenhill

Dr Kathryn Greenop, BA (Hons) (Psych), PhD (Psych)

Tess Gregory

Kristen Haas, BA

Jennifer Hafekost, BSocialSc, Grad Dip Ed

Katherine Hafekost, BSc(Hons)

Dr Erika Hagemann, BSc(Speech and Hearing Science)Hons, PhD

Dr Geoffrey Hammond, BSc, PhD

Kirsten Hancock, BA(Hons) MSc Candidate

Jessica Hall, B.Psych

Michèle Hansen, MPH, BSc

Annegret Harries

Natasha Haynes

Carly Herbison

Dr Siobhan Hickling, BSc, Grad Dip Diet, MPH, PhD

Sharon Hillman, B Psych, AMAPS

Emily Hockley, BSc

Anke Hoskins, Nurse, MPH

Derry Houston, BA/MSocWk

Dr Rae-Chi Huang, MB BS, PhD, FRACP (paeds), DCH

Anna Hunt, BEdu

Tanyana Jackiewicz, BSc(Hons) MPH

Peter Jacoby, BA(Hons), MSc

Angela Jacques

Caris Jalla

Khadra Jama-Alol BSc, PGradDip Biochem, MPH, PGradDip Pub Health

Dr Sarah Johnson, BA(Soc Sci), PostGradDip (Social Res), PhD

Heather Jones, B.Ed

Joan Jones

Rachel Jones

Dr Amanda Langridge, BSc (Math.Sci), BSc(Hons), PhD

Professor David Lawrence, BSc, PhD, ATCL

Amy Lee

Associate Professor Deborah Lehmann, MBBS, MSc

Assoc. Clin. Professor Helen Leonard, MBChB, MPH

Dr Jianghong Li, BA, MSc, PhD

Angela Kinnell

Faye Lim, BSc, BMedSci (Hons)

Sarah MacDermott, B.App.Sc (Speech & Hearing Science), M.A. (Education)

Jacqueline Mansour, BSc, MPH

Meg McHugh, BSc, MSc

Sally McIlroy

Mary McIllroy

Aoiffe McLoughlin BSc (Health Promotion) BBA

Heidi Meyer

Associate Professor Elizabeth Milne, BSc, MPH, PhD

Francis Mitrou, BEc

Ruth Monck, RN, RM

Dr Hannah Moore BSc(Hons1), GradDipClinEpid, PhD

Alani Morgan, TA EDWA

Jenny Mountain, BA, MBA

Virginia Muniandy, BEdu (Early Childhood)

Nada Murphy, BA, Grad Dip Psych, M App Psy

Dr Raewyn Mutch MB ChB, DipRACOG, FRACP, PhD

Dr Nusrat Naseem MBBS, MPH

Cathrine Nemer

Assoc. Prof. Wendy Oddy, BAppSci(Nutr), MPH, PhD

Melissa O'Donnell BPsych(Hons), MPsych, Grad Dip Ed, PhD, NHMRC Early Career Fellow

Dr Colleen O'Leary, RN, BSc, MPH, PhD

Ashleigh Owen, BA

Jan Payne SRN (UKCC), Post Grad Dip (Health Admin), MSc (Public Health)

Carol Philippe, RN

Shawn Phillips, BTh, MSWAP

Dr Terri Pikora, PhD

Anne Pugh

Jennifer Quick

Dr Tracy Reibel, BA (Hons), PhD

Wavne Rikkers, BA

Phil Riseborough, B.Psych ,M.Soc.

Deborah Robertson, BA, DipEd, Mphil

Dr Monique Robinson, PhD MPsych (Clinical) BA(Hons)Psych

Katherine Russell-Smith

Louisa Santucci

Elke Scheepers, BA, AdvCert Tvl Cons

Carrington Shepherd, BA (Econs)

Dr Adeleh Shirangi, PhD

Lorraine Sholson EN

Dr Rachel Skoss, PhD

Carolyn Smargiassi

Grant Smith, BPsych, M Psych

Kristy Staples, BA, Post Grad Dip Counsellor

Wenxing Sun, BHSc

Glenda Taylor, EN

Associate Professor Cate Taylor, BAppSc, PGradDipHlthSc, PhD, FSPA

Anna Urbanowicz,BSc(OT)(Hons)

Ellen Walker, BSocialWork (Hons)

Alicia Watkins, BPsych, PGradDip(Psych)

Dr Rochelle Watkins BSc (Physio), PhD, GradDipMgnt

Linda Watson

Felicity Watt, B.Psych, MSc

Meredith West

Dr Andrew Whitehouse, BSc (Human Communication Science), PhD

Dr Amanda Wilkins MBBS, FRACP, MPH

Kingsley Wong, MBBS MBA MSc AFCHSM, MPH candidate, UWA

Dianne Wood, BAppSc(Phys Ed)Dip Ed, Grad Dip HN

RESEARCH SUPPORT STAFF

Helen Daley

Colette Newcomb

Leanne Scott

Kathryn Wilson

POSTGRADUATE STUDENTS

Alison Anderson, BSc (Hons), GradDipPH, PhD candidate, UWA

Alicia Annamalay, Hons candidate, UWA

Oyekoya Ayonrinde, PhD candidate, UWA

Helen Bailey, PhD candidate, UWA

Katherine Bathgate, BSc (Nutr & Food Sc),

Grad Dip Diet, Grad Cert Teach, MPH, APD, PhD candidate, Curtin

Ami Bebbington, BSc (Hons), MBioStats candidate, University of Melbourne

Sara Beckett, PhD candidate, UWA

Sally Brinkman, BA, MPH, PhD candidate, Curtin

Adele Cox, Diploma (Broadcasting and Journalism), Masters candidate, UWA

Lyn Colvin, PhD candidate, UWA

Sophie Davidson, Hon candidate, ECU

Aditya Deshpande, BDS, PhD candidate, UWA

Jan de Groot, MPH, PGDipNursing (Midwifery), BAppSc(Med Tech), RN, RM, NNT, CHN, PhD candidate, UWA

Jenny Fairthorne, Msc, MPH, PhD candidate, UWA

Stephanie Fehr, BSc, BMedSci (Hons), PhD candidate, UWA

Nicola Fenelon, Masters Candidate, UWA

Anna Ferrante BA (Mathematics), Dip Ed, PhD candidate

Kitty-Rose Foley, BSc (OT) (Hons), PhD candidate, ECU

Kathryn France, BSc(Hons), PhD candidate, ECU

Noula Gibson, BAppSc(Physio)(Hons), M Physio(Develop Paeds), PhD candidate, UWA

Michèle Hansen, MPH, BSc, PhD candidate, UWA

Aveni Haynes, Masters/PhD candidate, UWA

Lauren Hollier, PhD candidate, UWA

Katrina Hopkins, BAppSci(Psych), DipEd(Psych), MAppSci(Health Sciences), PhD candidate, UWA

Amanda Jefferson, BSc, PhD candidate, Curtin

Christine Jeffries-Stokes, MBBS, MPH, PhD candidate, UWA

Jocelyn Jones, BA (Sociology), EN, MAE, PhD candidate, UWA

Kellie Jones, PhD candidate, ECU

Milena Jokic, PhD candidate, UWA

Brilliana von Katterfeld BA BSc(Hons) PhD candidate, UWA

Olivia Knight, PhD candidate, ECU

Matthew Legge, PhD candidate, UWA

Lucy Lewis, PhD candidate, UWA

Faye Lim, Hons candidate, UWA

Sandra Louise, PhD candidate, UWA

Miriam Maclean, PhD candidate, UWA

Geraldine Maibani-Michie, PhD candidate, University of Qld

Aoiffe McLoughlin BSc (Health Promotion) BBA Master of Public Health

Francis Mitrou, PhD Candidate, UWA

Hannah Moore, BSc(Hons1), GradDipClinEpid, PhD candidate, UWA

Jenny Mountain, BA, MBA, Masters candidate, UWA

Dr Maryam Mozooni, (MD) PhD candidate, UWA

Barbara Nattabi, PhD candidate, Curtin

Dr Anett Nyaradi, PhD candidate, UWA

Mr Ramin Nikravan, DPH candidate, Curtin

Afrooz Njafzadeh, PhD candidate, UWA

Jan Payne, SRN(UKCC),PGradDip(Hlth Admin), MSc(Pub Hlth), PhD candidate, UWA

Glenn Pearson, BA(Education), PhD candidate, UWA

Gavin Pereira, MAppStat(Dist) BCM(Hons) GCert Res Comm, PhD candidate, UWA

Shawn Phillips, BTh, MSWAP,PhD candidate, UWA

William Pomat, BSc (Hons), MSc, PhD candidate, UWA

Carrington Shepherd, BSc, PhD candidate, Curtin

Dr Desiree Silva, MBBS, FRACP, MPH, PhD candidate, UWA

Jessica Simons, PhD candidate, UWA

Lydia Sung, PhD candidate, UWA

Lauren Taylor, PhD candidate, UWA

Jessica Tearne, PhD candidate, UWA

Anna Urbanowicz, BSc(OT)(Hons), PhD candidate, ECU

Sian Williams, PhD candidate, UWA

Janice Wong, BSc (Psych) (Hons), PhD candidate, UWA

Kingsley Wong, MBBS MBA MSc AFCHSM, MPH candidate, UWA

Paula Wyndow, BSc Postgraduate Diploma, PhD candidate, Curtin

Theses passed

Helen Bailey PhD, University of Western Australia: The relationship between environmental exposures and the development of acute lymphoblastic leukemia in children

Sophia Davidson BSc (OT) (Hons), Edith Cowan University: The employment patterns of young adults with intellectual disability living in Queensland

Robyn Earl BSc (OT) (Hons), Edith Cowan University: A normative study of the participation patterns of young adults living in Western Australia

Nicola Fenelon, Master of Clinical Psychology, University of Western Australia: Maternal stress in pregnancy and brain functions in adolescence.

Jessica Hall, Master of Clinical Psychology, University of Western Australia: Mental health in children and adolescents from culturally and linguistically diverse backgrounds.

Brilliana Katterfeld PhD, University of Western Australia: Perinatal health in children from culturally and linguistically diverse backgrounds in Western Australia

Matthew Legge PhD, University of Western Australia: The genetic epidemiology of melanocytic naevi

Hannah Moore PhD, University of Western Australia: Epidemiological perspectives of acute lower respiratory infections in young Western Australian Aboriginal and non-Aboriginal children

Barbara Nattabi PhD, Curtin University: Fertility desires and intentions of HIV Positive Men and Women in Post-conflict Northern Uganda

Ramin Nikravan Doctorate of Public Health, Curtin University of Technology: Antioxidant and omega-3 fatty acid intake in the modulation of respiratory illness and asthma in children

Gavin Pereira PhD, University of Western Australia: The influence of traffic-related air pollution on infant and child health: an application to fetal growth and asthma

William Pomat PhD, University of Western Australia: Mucosal immunity to Streptococcus pneumonia

Melissa Scott BSc (OT) (Hons), Edith Cowan University: The meaning of a good life for young adults living with Down syndrome

Awards

Carol Bower, Life Membership, Australasian Epidemiological Association

Jenny Downs, Heath Ledger Career Development Award, Telethon Institute for Child Health Research, November 2011

Jenny Fairthorne, Australian Postgraduate Award 2011

Jenny Fairthorne, UWA Safety Net Top-up Scholarship 2011

Stephanie Fehr, Australian Postgraduate Award 2011

Stephanie Fehr, UWA Safety Net Top-up Scholarship 2011

Kitty-Rose Foley, Mary Walters Bursary from the Graduate Women of Western Australia, Travel Award 2011

Kitty-Rose Foley, Family Special Interest Research Group Fellowship to support travel to IASSID, Nova Scotia, Halifax

Helen Leonard, Author of UWA's highly cited papers 2010

Miriam Maclean, The Australian Postgraduate Award

Miriam Maclean, The UWA Safety Net Top-Up Scholarship

Elizabeth Milne, Telethon Institute for Child Health Research Leadership Award

Anett Nyaradi. The Raine Study PhD Student Top Up Scholarship

Melissa O'Donnell, Science meets Parliament – NHMRC Attendee and Travel Award

Melissa O'Donnell, Australian Academy of Science – NHMRC Early Career Research Award, Attendance at Science at the Shine Dome

Jan Payne, Public Health Association of Australia WA Branch Community Award, November 2011

Gavin Pereira, Jan Watt Memorial Prize for Excellence in Public Health Field Research, Faculty of Medicine and Dentistry UWA

Monique Robinson, Raine Medical Research Foundation Prize for Best Poster Presentation

Monique Robinson, Heath Ledger Career Development Award

Monique Robinson, Australian Psychological Society Early Career Research Award

Monique Robinson, UWA Outstanding Young Investigator Award

Monique Robinson, Qantas New Investigator of the Year Award

Monique Robinson, WA Winner Young Tall Poppy Science Award

Monique Robinson, UWA Prize for Higher Degree by Research Achievement (Special Commendation)

Monique Robinson, Heart Foundation of Australia Travel Grant

Anna Urbanowicz, Australian Postgraduate Award 2011

Janice Wong, The Australian Postgraduate Award

Janice Wong, The Stan and Jean Perron Award

External Committees

INTERNATIONAL

Carol Bower, International Clearinghouse for Birth Defects Surveillance and Research Nominating Committee 2011-2012

Helen Leonard, Member of Autism Speaks International Autism Epidemiology Network Workgroup, (2007-)

Helen Leonard, Member of Executive of RettSearch, International Consortium of Rett Syndrome Clinical Researchers (2009-)

Jianghong Li. Rural Sociology published by the American Rural Sociological Society, Associate Editor (June 2005-2011)

Elizabeth Milne, Deputy Chair, Management Committee of the Childhood Leukaemia International Consortium (2006-)

Elizabeth Milne, Working party for the development of international studies of embryonal cancers in children, WHO International Agency for Research into Cancer, Lyon, France (2006-)

Elizabeth Milne, Brain Tumour International Consortium (BTEC), (2010-)

Elizabeth Milne, International Childhood Cancer Cohort Consortium (I4C), (2010-)

Elizabeth Milne, Scientific Programme Advisory Committee for the International Society for Paediatric Oncology (SIOP) in London 2012 and Hong Kong 2013 (Invited)

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

Carol Bower, National Perinatal Statistics Unit Steering Committee for Congenital Anomalies

Carol Bower, Australian Paediatric Surveillance

Unit Scientific Review Panel

Carol Bower, Australian Paediatric Surveillance Unit Board Chair

Carol Bower, National Perinatal Epidemiology and Statistics Unit Fetal Alcohol Spectrum Disorder

Rebecca Glauert, International Data Linkage Conference Organising Committee. Deputy Chair (2010 – present)

Rebecca Glauert, International Data Linkage Conference Scientific Committee (2010 – present)

Deborah Lehmann, Data safety monitoring board of the PneuMum Maternal pneumococcal immunisation study in Northern Territory (2005-)

Helen Leonard, Member of Executive, Australian Association of Developmental Disability Medicine, (2002-)

Elizabeth Milne, Conference Organising Committee for the Annual Australasian Epidemiology Association Scientific meeting, Perth WA 2011

Raewyn Mutch, RACP Chapter of Community Child Health, Share WebSite Contributor

Catherine L Taylor, Intensive Nurse Home Visiting (INHV) Project (ARACY and the Centre for Community Child Health), Member of the Expert Reference Group

Catherine L Taylor, ARACY State Convenor (WA)

Catherine L Taylor, Australian Research Alliance for Children and Youth (ARACY), Councillor

Catherine L Taylor, New Investigators Network, Australian Research Alliance for Children and Youth (ARACY), Mentor

Catherine L Taylor, International Journal of Speech-Language Pathology, Member of the Executive Board

LOCAL

Carol Bower, Perinatal and Infant Mortality Committee Department of Health WA

Carol Bower, Prenatal Diagnosis Committee, Department of Health WA

Jenny Bourke, Committee member, Board of Management, Parents of Children with Disabilities (Inc), Kalparrin

Jenny Bourke, Member of Scientific Advisory Council, SIDS and Kids WA

Jenny Downs, Human Research Ethics Committee, Princess Margaret Hospital for Children (2010-)

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

Rebecca Glauert, Data Linkage Advisory Board (2010 – present)

David Lawrence, Heathway Research Committee, (2010-)

Deborah Lehmann, Perinatal and Infant Mortality Committee, Ministry for Health, WA, Deputy to Carol Bower (2005-)

Deborah Lehmann, Meningitis Centre Management Committee

Helen Leonard, Women's and Newborns' Health Network Executive Advisory Group

Helen Leonard, Executive Committee Perth Epidemiology Group, (2008-)

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

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

Elizabeth Milne, Cancer Council Western Australia Research Sub-Committee

Hannah Moore, Meningitis Centre Management Committee

Hannah Moore, Australasian Epidemiological Association 2011 Conference Organising Committee – Secretary

Monique Robinson, Scientific Advisor to Commissioner for Children and Young People, WA

Monique Robinson, Scientific Committee Member for the 7th World Conference on the Promotion of Mental Health and the Prevention of Mental and Behavioural Disorders, Perth Australia

Desiree Silva, Head of Department Medical Advisory Committee (HOD/MAC) Joondalup Health Campus

Rochelle Watkins, Member, Board of Directors, Neurological Council of Western Australia

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

Invited Presentations

INTERNATIONAL

Anna Ferrante, Using Health Data to Determine Gender and Race Differences in the Risk Factors Associated with Delinquency. SHIP Conference, St Andrews, Scotland, September 2011

Kitty-Rose Foley, To feel belonged: The voices of children and youth with disabilities on the meaning of wellbeing. 5th Asia Pacific Occupational Therapy Congress, Chiang Mai, Thailand, November 2011

Deborah Lehmann, Invited speaker on tour of USA in 2011 – New York University; Merck & Co, Pennsylvania; Case Western University, Cleveland; Washington University, St Louis; University of Washington, Seattle

Jianghong Li. Modernity's paradox and child health and wellbeing in developed countries. Invited Lecture Yunnan Health and Development Research Association, Kunming, Yunnan, China, March 2012 (accommodation, local transport and food paid by the host).

Jianghong Li. Causes of rising trends in poor child outcomes and strategies for reversing them. Invited speech at the Eighth Shanghai International Forum for Children, Shanghai 2-3 August 2011 (accommodation, local transport and food paid by the host).

Raewyn Mutch, Vancouver FASD 4th Biennial Conference: Overview of FASD in Australia, March 2011

Monique Robinson, Maternal pre-pregnancy body weight and risk for affective disorders in

offspring; Infants born at 37 weeks' gestation are at increased risk for behavioural problems through to adulthood. Developmental Origins of Health and Disease (DOHaD) International Conference (Portland, US): 18th-21st September 2011

NATIONAL

Jenny Downs, Initial assessment of the StepWatch Activity Monitor™ to measure walking activity in Rett syndrome. 3rd National Australian Physiotherapy Association Conference, Brisbane, October 2011

Stephanie Fehr, The CDKL5 disorder: a new cause of early-onset encephalopathy. 25th Epilepsy Society of Australia Annual Scientific Meeting, Brisbane, November 2011

Kitty-Rose Foley, Functioning of young adults with Down syndrome transitioning into post school day occupations. Occupational Therapy Australia 24th National Conference and Exhibition, Gold Coast, Queensland, June/July 2011

Rebecca Glauert, WA Developmental Pathways Program: An overview and outcomes. New Horizons for Educational Research, Adelaide, September 2011.

Heather Jones, Alcohol and Pregnancy Research in Australia, Alcohol and Pregnancy Community Conversation, Cairns, February 2011

Helen Leonard, The value of a population database in the understanding of a rare genetic disorder: insights from AussieRett, Brisbane, October 2011

Elizabeth Milne, Nutrition and Genome Health in Children, Royal Brisbane & Women's Hospital Health Care Symposium, Brisbane October 2011

Elizabeth Milne, Dietary factors contributing to risk or prevention of childhood cancer, official launch of the Children's Health and Environment Program at the University of Queensland, Brisbane, August 2011

Raewyn Mutch, FASD Training and Seminars: Anyinginyi Health Aboriginal Corporation, Tennant Creek, NT, December 2011

Raewyn Mutch, FASD Training and Seminars: Drug Education Network, Hobart, Tasmania, December 2011

Raewyn Mutch, FASD Training and Seminars: Health Ed/ Generation Next, RACGP Accredited, Sydney, NSW

Melissa O'Donnell, Rising parental mental health issues and the impact on child maltreatment risk. International Mental Health Congress, Brisbane, August 2011

Ellen Walker, Carers, emergent adults, and society: carers' experience of transition as their daughter with Rett syndrome transitions from late adolescence to adulthood. Australasian Society for Intellectual Disability Conference, Glenelg, November 2011

LOCAL

Alison Anderson, AussieRett & InterRett collaborations with China, Presentation to delegation from the Shanghai People's Association for Friendship with Foreign Countries (SPAFFC), Perth, November 2011

Katherine Bathgate, Maternal mental health and diagnosis of autism in Rett syndrome. Disability Services Commission, Perth, October 2011

Katherine Bathgate, Fussy eaters to healthy eating: strategies to prevent nutritional deficiencies. Nutrition Australia, Perth, October 2011

Jenny Bourke, IDEA database and Down syndrome research. Disability Services Commission. October 2011

Carol Bower, Alcohol and Pregnancy, Perinatal Symposium, Joondalup Health Campus

Carol Bower, WA Register of Developmental Anomalies, Perinatal Symposium, Joondalup Health Campus

Carol Bower, Collaborating with consumers: a case study in success and satisfaction. Australasian Epidemiological Association Annual Conference

Carol Bower, Consumer participation – a researcher's perspective. University of Western Australia, School of Population Health Summer School Consumer and Community Participation in Health and Medical Research: A training workshop for researchers

Jenny Downs, Medical issues in Rett syndrome. Disability Services Commission Nurses Study Day, Perth, March 2011

Jenny Downs, AussieRett & InterRett collaborations with China, Presentation to delegation from the Shanghai People's Association for Friendship with Foreign Countries (SPAFFC), Perth, November 2011

Stephanie Fehr, The CDKL5 disorder: a new cause of early-onset encephalopathy. Child and Adolescent Health Research Symposium, Perth, October 2011

Anna Ferrante, Dimensions of Delinquency: Differences in risk factors for delinquency across sub-populations in Western Australia. WA Department of Corrective Services, Perth, November 2011

Geoffrey Hammond, Describing trends in gestational age, maternal age, and preterm birth rates in Western Australia from 1984 to 1999. Australasian Epidemiological Association Annual Conference 2011 - Combining Tradition and Innovation, Perth, September 2011

Geoffrey Hammond, Child and Adolescent Health Research Symposium, Perth, October 2011

Heather Jones, The Development of a Screening and Diagnostic Instrument for FASD in Australia, Child and Adolescent Health Research Symposium, Perth, October 2011

Amanda Langridge, Multinational registry-based analyses of autism risk factors and trends: the International Collaboration for Autism Registry Epidemiology (iCARE). Australasian Epidemiological Association Annual Conference 2011 - Combining Tradition and Innovation, Perth, September 2011

Amanda Langridge, Maternal conditions and

Perinatal Characteristics Associated with Autism Spectrum Disorder and Intellectual Disability. Australasian Epidemiological Association Annual Conference 2011 - Combining Tradition and Innovation, Perth, September 2011

Amanda Langridge, Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability. Child and Adolescent Health Research Symposium, Perth, October 2011

David Lawrence, Physical health of people with mental illness. Unlocking the door to health and wellbeing: where do we find the key? Webinar for Schizophrenia Awareness Week, Perth, 2011

David Lawrence, Relating data to events and trends concerning suicide. Prevalence, prevention and early response to suicide, Perth, March 2011

Helen Leonard, Autism and intellectual disability are differentially related to socio-demographic background at birth. Asia Pacific Autism Conference, Perth, September 2011

Helen Leonard, Multi-national registry based analyses of autism risk factors and trends: The International Collaboration for Autism Registry Epidemiology (ICARE). Asia Pacific Autism Conference, Perth, September 2011

Faye Lim, Rett syndrome in China: Barriers to diagnosis and care. Child and Adolescent Health Research Symposium, Perth, October 2011

Faye Lim, AussieRett & InterRett collaborations with China, Presentation to delegation from the Shanghai People's Association for Friendship with Foreign Countries (SPAFFC), Perth, November 2011

Raewyn Mutch, FASD Seminars: South West Foster Families, February 2011

Raewyn Mutch, McCusker Centre for Action on Alcohol and Youth: "How alcohol affects my work"

Raewyn Mutch, FASD: School Psychologist Association Annual Conference, Perth WA 2011

Raewyn Mutch, FASD: Psychologists of Juvenile Justice, Department of Corrective Services, Perth

Raewyn Mutch, FASD: Professional Development Day, Child and Community Health, DoH

Raewyn Mutch, FASD: Princess Margaret Hospital Grand Round

Melissa O'Donnell, Rising parental mental health issues and the impact on child maltreatment risk. Australian Epidemiological Association Annual National Conference, Perth, September 2011

Monique Robinson, Prenatal stress events and behavioural development from age two to 14 years: The influence of the number, type and timing of stressful life experiences. Australasian Marce Society Conference Perth, 13th-14th October 2011

Amanda Wilkins, FASD Seminars: South West Foster Families, February 2011

Active collaborations

INFECTIOUS DISEASES GROUP

David Smith, PathWest Laboratory Medicine, Perth WA

Anthony Keil, Department of Microbiology, Princess Margaret Hospital, Perth WA

Peter Richmond, Chris Blyth, School of Paediatrics and Child Health, UWA, Perth WA

Anne Mahony and Charles Douglas, Population Health, WA Country Health Services – Goldfields WA

Bega Garnbirringu Health Services, Kalgoorlie WA

Harvey Coates and Francis Lannigan, ENT Specialists, Princess Margaret Hospital for Children, Perth WA

Sharon Weeks, Professional Hearing Services, Perth WA

Christine Jeffries-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, Communicable Disease Control Directorate, Department of Health, Perth WA

Ngunytju Tjitji Pirni Inc, Kalgoorlie WA

Allan Cripps, Gold Coast Campus, Griffith University, Qld

Helen Smith, Public Health Microbiology, Public Health Microbiology, Forensic and Scientific Services, Coopers Plains, Qld

Peter Siba, William Pomat, Andrew Greenhill, Suparat Phuanukoonnon, Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea

Eileen Dunne, Catherine Satzke, Murdoch Children's Research Institute, Melbourne Vic

Anita H. J. van den Biggelaar, Crucell, The Netherlands

Kylie Carville, Epidemiology Unit, Victorian Infectious Diseases Reference Laboratory, Melbourne Vic

Gillian Hall, National Centre for Epidemiology and Population Health and Medical School, Australian National University, Canberra ACT

Jennelle Kyd, Central Queensland University

Trevor Duke, Centre for International Health, University of Melbourne

Megan Passey, University Centre for Rural Health-North Coast, University of Sydney

Heath Kelly, Epidemiology Unit, Victorian Infectious Diseases Reference Laboratory, Melbourne Vic

David Burgner, Infection, Immunity & Environment, Murdoch Children's Research Institute, Melbourne Vic

CHILDHOOD CANCER

Patricia Buffler, University of California, Berkeley USA

Catherine Mettayer, University of California, Berkeley USA

Jacqueline Clavel Inserm, CESP Centre for research in Epidemiology and Population Health, U1018, Environmental epidemiology of cancer Team, F-94807, Villejuif, France; Univ Paris-Sud, UMRS 1018, F-94807, Villejuif, France

Claire Infante-Rivard Mcgill University& Centre Universitaire Mere-Enfant Sainete-Justine, Quebec, Canada

Eve Roman Department of Health Science, University of York, UK

Logan Spector Division of Epidemiology/ Clinical Research, Department of Pediatrics and Masonic Cancer Center, University of Minnesota, USA

Sergio Koifmann National School of Public Health, Oswaldo Cruz Foundation (FIOCRUZ), Ministry of Health, Rio de Janeiro, Brazil

Maria Pombo d'Oliviera, Pediatric Hemotology-Oncology Program, Instituto Nacional do Cancer, Rio de Janeiro-Brazil

Eleni Petridou, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens, Athens, Greece

Joachim Schuz, International Agency for Research on Cancer (IARC), Section of Environment and Radiation, Lyon, France

John Dockerty, Department and Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, New Zealand

Michael Fenech, CSIRO Nutrigenomics, Adelaide.

Bruce Armstrong, Sydney School of Public Health, University of Sydney, NSW

Frank van Bockxmeer, Royal Perth Hospital, WA

Michelle Haber, Children's Cancer Institute Australia, NSW

Rodney Scott, Hunter Medical Research Institute, University of Newcastle, NSW and Hunter Area Pathology Service, NSW

John Attia, Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, NSW, Department of Medicine, John Hunter Hospital and Hunter Medical Research Institute, NSW

Murray Norris, Children's Cancer Institute Australia, NSW

Lin Fritschi, WA Institute for Medical Research, University of Western Australia, WA

Margaret Miller, Edith Cowan University, WA

Judith Thompson, WA Cancer Registry,WA

Frank Alvaro, John Hunter Hospital, Newcastle, NSW

Catherine Cole, Princess Margaret Hospital for Children, WA

Luciano Dalla Pozza, Children's Hospital at Westmead, NSW

John Daubenton, Royal Hobart Hospital, Tasmania

Peter Downie, Monash Medical Centre, Melbourne, Victoria

Liane Lockwood, Royal Children's Hospital, Brisbane, Queensland

Maria Kirby, Women's and Children's Hospital, Adelaide, SA

Glenn Marshall, Sydney Children's Hospital, Sydney, NSW

Elizabeth Smibert, Royal Children's Hospital, Melbourne, Victoria

Ram Suppiah, Mater Children's Hospital, Brisbane, Queensland

LOOKING AT LANGUAGE

Mabel L Rice, University of Kansas, USA

Shelley Smith, University of Nebraska Medical Centre, USA

Javier Gayan, Neocodex, Spain

HUMAN CAPABILITY

Linda Harrison, Charles Sturt University, New South Wales.

Raine study team including Martha Hickey, Department of Obstetrics and Gynaecology. University of Melbourne, Victoria.

Rebecca Giallo, Fabrizio D'Esposito, Parenting Research Centre, Victoria.

Sybille McKeown, Australian Bureau of Statistics, ACT.

Suzy Saw, Department of Health and Ageing, ACT.

Donna Berthelsen, Queensland University of Technology, QLD.

Ben Edwards, Australian Institute of Family Studies, Victoria.

Jan Nicholson, Murdoch Childrens Research Institute, Victoria.

Megan Shipley, Australian National University, ACT.

David Zarb, Playgroup WA (Inc), WA.

Jason Connor, University of Queensland, QLD .

Marty Cooke, University of Waterloo, Canada.

Steve Kisely, University of Queensland, QLD.

Sharon Lawn, Flinders University, SA .

Sybille McKeown, Australian Bureau of Statistics, ACT.

Alex Mitchell, University of Leicester, United Kingdom.

David Povah, Australian Bureau of Statistics, WA.

Dr Krysta Boylan (McMaster University, Canada)

A/Prof. David Burgner (Murdoch Children's Research Institute, Melbourne)

A/Prof. Peter Franklin (School of Population Health, University of Western Australia)

A/Prof Renee Goodwin (Columbia University, USA)

Prof. Roger Hart (School of Women's and Infants' Health, University of Western

Australia)

Prof. Stephen Lye (Canadian Institute Health Research, Canada)

A/Prof. S. Rachel Skinner (University of Sydney, Sydney)

Dr Ryan J. Van Lieshout (McMaster University, Canada)

BIRTH DEFECTS

Australian FASD Collaboration. Lead Investigators Winthrop Research Professor Carol Bower and Professor Elizabeth Elliott AM, Steering group of health professionals, researchers, epidemiologists and consumers and community members

INTELLECTUAL DISABILITY

University of Aarhus, Denmark.

Dr Gordon Baikie, Royal Children's Hospital, Melbourne.

Dr Xinhua Bao, Department of Paediatrics and Obstetrics, Peking University First Hospital, Beijing, China.

Dr Michaeline Bresnahan, Columbia University, New York, USA.

Dr Julie Briody, Department of Nuclear Medicine, The Children's Hospital at Westmead, Sydney.

David Burgner, Murdoch Children's Research Institute, VIC 3052 Australia.

Dr Ron Chalmers, Disability Services Commission WA, Directors General Steering Committee, Developmental Pathways Project, TICHR.

Prof John Christodoulou, Children's Hospital, Westmead, NSW.

Columbia University, New York, USA.

The Children's Hospital at Westmead.

Dr Mark Davis, Royal Perth Hospital, Perth.

Dr Carolyn Ellaway, Children's Hospital, Westmead, NSW.

Prof Elizabeth Elliott, Paediatrics & Child Health, Children's Hospital, Westmead, FASD Collaboration.

Katheryn Frame, The International Foundation for CDKL5 Research, USA.

Dr Michael Freilinger, University of Vienna, Austria.

Prof Sue Fyfe, Faculty of Health Science, Curtin University, Perth.

Prof Elizabeth Geelhoed, School of Population Health, UWA.

Dr Mika Gissler, THL National Institute for Health and Welfare, Helsinki, Finland.

Dr Raz Gross, Columbia University, New York, USA.

Ronnie Hagan, Department of Neonatology, School of Women's and Infants' Health, UWA, Perth.

Dr Kylie Hill, School of Physiotherapy, Curtin University, Perth.

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Institute of Psychiatry, London, UK.

Julie Ireland, Down Syndrome WA

Biostatistics, Karolinska Institutet, Stockholm, Sweden.

Prof Walter Kaufmann, Center for Genetic Disorders of Cognition and Behavior, Kennedy Krieger Institute and Johns Hopkins University School of Medicine, Baltimore, UWA.

Gwynnyth Llewellyn, University of Sydney, Sydney.

Prof Nick Lennox, University of Queensland, Queensland.

Dr Meir Lotan, Israeli Rett Centre, Tel Aviv, Israel.

Prof Vera Morgan, University of Western Australia.

Dr Lakshmi Nagarajan, Department of Neurology, Princess Margaret Hospital, Perth.

Dr Natasha Nassar, Kolling Institute of Medical Research, University of Sydney.

Norwegian Institute of Public Health, Oslo, Norway.

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Dr Eric Parner, University of Aarhus, Denmark.

Dr Alan Percy, University of Alabama, USA.

Dr Mercè Pineda, Centro Médico Teknon and Sant Joan de Déu Hospital, Barcelona, Spain.

Dr Rohit Pokharel, Muscular Dystrophy Foundation, Kathmandu, Nepal.

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Dr Teresa Temudo, Hospital Geral de Santo Antonia, Porto, Portugal.

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Dr Michael Vitale, Morgan Stanley Children's Hospital of New York, New York, USA.

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and Padiatric Rehabilitation, Princess Margaret Hospital, Perth.

Dr Ingergerd Witt-Engerstrom, Swedish Rett Centre, Sweden.

Dr Helen Woodhead, Sydney Children's Hospital, New South Wales.

Dr Xiru Wu, Department of Paediatrics and Obstetrics, Peking University First Hospital, Beijing, China.

Dr Bruria Ben Zeev, Pediatric Neurology, Safra Pediatric Hospital, Tel Hashomer, Israel.

DEVELOPMENTAL PATHWAYS PROJECT

ARACY New Investigator Network, National Collaboration

Assoc Prof Leah Bromfield, Australian Centre for Child Protection, University of South Australia, Adelaide, Australia

Prof Marni Brownell, University of Manitoba, Manitoba Centre for Health Policy, Canada

Prof Jane Fisher, The Jean Hailes Foundation, Monash University, Victoria, Australia

Prof Ruth Gilbert, University College London, Institute of Child Health, United Kingdom

Dr Steven Guthridge, Department of Health and Community Services, Northern Territory, Darwin, Australia

Dr Daryl Higgins, Australian Institute of Family Studies, Melbourne, Australia

Dr Melissa Kaltner, Queensland Health, Brisbane, Australia

Dr Kirsten McKenzie, Queensland University of Technology, Brisbane, Australia

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SOCIAL DETERMINANTS OF CHILD HEALTH/ SOCIAL EPIDEMIOLOGY

Associate Professor Wen-Jui Han, School of Social Work, Columbia University, the US

Professor Joachim Singelmann, Department of Sociology, Louisiana State University, the US

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Dr Garth Kendall, School of Nursing and Midwifery, Curtin University

Professor Bev McNamara, School of Occupational Therapy and Social Work, Curtin University

VACCINE TRIALS GROUP

Overview

During 2011 our new studies included of an Australian designed Ross River Virus vaccine in adults, and a new vaccine for the prevention of Meningococcal B disease in adolescents. A number of important vaccine studies have also continued this year including the Dengue Fever, Human Papillomavirus (HPV), Respiratory Syncitial Virus (RSV), Meningococcal B, Avian Influenza, influenza vaccine effectiveness in young children (WAIVE) and the Pertussis vaccine at Birth study.

Highlights from 2011 must include the conclusion of the first-in-man *Staphylococcus aureus* (Golden Staph) vaccine study in adults that was presented at an international conference in Italy. Another achievement has been the success of the FAST study, which monitored the safety of the 2011 Influenza vaccine in children. This study, sponsored by the Health Department of WA, came about because of high fevers and an increased incidence of convulsions experienced by children < 5 years during 2010 with the use of Fluvax. The results showed that the adverse events following influenza vaccination in 2010 were not observed during 2011, which was reassuring for both health professionals and parents. We also continue to be involved in the national vaccine safety surveillance through the PAEDs program as well as the WA Vaccine Safety Surveillance System. Ensuring vaccines remain safe in those who use them continues to have a high priority in our research activities.

It has been an exciting year in the respiratory infectious disease group with several new scientific publications and international conference presentations of our work here in VTG. We have expanded from focusing on ear, nose and throat infections into chronic lung disease in both adults and children. These new areas are being explored as the host-bacterial interactions appear very similar between these different types of disease. This is also the first time in which we are able to take some of the research we have done in the laboratory and apply it in the clinic with the establishment of the Dornase alfa trial for which recruitment will begin in 2012.

VTG has continued to be actively involved in the areas of vaccine safety, pneumococcal infection and neonatal immunity. Our staff members have presented data at international conferences during 2011, published in high impact journals and have also secured ongoing funding for our research.

Immunisation

A PHASE L/LL STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF A VERO CELL-DERIVED WHOLE VIRUS H5N1 INFLUENZA VACCINE IN HEALTHY INFANTS, CHILDREN AND ADOLESCENTS AGED 6 MONTHS TO 17 YEARS.

Associate Professor Peter Richmond

Influenza is a viral infection that frequently causes severe disease. The disease can cause sudden onset of general and breathing symptoms (for example headache, muscle pain, chills, fever, shortness of breath, sore throat, cough and runny nose).

The main purpose of the study is to determine 1) How safe the vaccine is and which side effects may occur in children and 2) Whether the immune system produces special proteins called antibodies against the flu virus strain in the vaccine

The required number of subjects for the study was achieved on the 09th September 2011.

At VTG eleven subjects have been recruited. Ten subjects are enrolled in Stratum A with one subject enrolled in Stratum B. All visits and study procedures have been completed

Funders of the project - Baxter

LOT-TO-LOT CONSISTENCY AND BRIDGING STUDY OF A TETRAVALENT DENGUE VACCINE IN HEALTHY ADULTS IN AUSTRALIA

Associate Professor Peter Richmond

Dengue is a disease caused by a 4 types of a virus that is transmitted by mosquito bites. People who catch the dengue virus may get “dengue fever” – fever up to 40°C for 2 to 7 days, often with severe headache, vomiting, muscle and joint pains, pain behind the eyes, and skin rash. Dengue is sometimes more severe and can cause bleeding and/or a sudden fall in blood pressure (shock). Dengue can cause death in some cases, mainly in children.

There are no vaccines and no specific treatments presently available against the disease.

The purpose of this research study is to see if four different batches of the study vaccine produce a similar antibody response and to continue to assess the safety of the vaccine.

Recruitment for this study commenced in October 2010 and 74 subjects were recruited to this site. This study should be completed in 2012.

Funders of the project - Sanofi Pasteur SA

A PHASE III, DOUBLE-BLIND, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE SAFETY, IMMUNOGENICITY AND EFFICACY OF GLAXOSMITHKLINE BIOLOGICALS’ HPV 16/18 L1/AS04 VACCINE ADMINISTERED INTRAMUSCULARLY ACCORDING TO A THREE-DOSE SCHEDULE (0, 1, 6 MONTH) IN HEALTHY ADULT FEMALE SUBJECTS AGED 26 YEARS AND ABOVE.

Dr Tanya Stoney and Associate Professor Rachel Skinner

Human papilloma viruses (HPV) are viruses that cause a common infection of the skin and genitals in men and women. Several types of HPV infection are transmitted by sexual contact and, in women, can infect the cervix (the lower part of the uterus or womb). This infection often goes away by itself. However, if it does not go away (this is called persistent infection), it can lead over a long period of time to cancer of the cervix. If a woman is not infected by HPV, it is very unlikely that she will get cervical cancer. Two types of HPV, called HPV-16 and HPV-18, cause about 70 percent of the cases of cervical cancer in the world. Consequently, a vaccine able to prevent HPV infections would be of great value in the protection against cervical cancer.

GSK Biologicals has developed a vaccine against HPV types 16 and 18. This HPV vaccine has been tested in thousands of young women in different countries, and the reactions observed with the injection of the vaccine to date have been similar to those seen after vaccination with other common vaccines. These studies have also shown that the vaccine stimulates defences against the viruses, e.g. production of antibodies (substances made by your body to prevent infections). It has also been shown that the vaccine prevents persistent infections with HPV-16 or -18 and associated pre-cancerous abnormalities (this is called vaccine "efficacy"). Although pre-teen and adolescent girls represent an important target population for preventive HPV vaccination, vaccination should also be made available to adult women. This study is therefore designed to evaluate the immune responses, safety and efficacy of the investigational HPV vaccine in women who are 26 years of age or older.

The sixth year of the Cervarix HPV vaccine trial for women aged over 26 years commenced in 2011. One hundred and fifty women were recruited into this study at VTG. The purpose of this study is to determine the efficacy, safety and immunogenicity of Cervarix in older women. Currently the HPV-16/18 vaccine (Cervarix) is licensed in over 100 countries world wide, 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; however it is still important that the current studies are completed to determine the efficacy of the vaccine in older women which can then be used for cost effectiveness modelling.

Funders of the project – GlaxoSmithKline

A PHASE IIIB, OPEN, MULTI CENTRE GYNAECOLOGICAL EXTENSION STUDY FOR FOLLOW-UP OF A SUBSET OF 580299/008 STUDY SUBJECTS WHO WERE EITHER CERVICAL CYTOLOGY NEGATIVE AND ONCOGENIC HPV POSITIVE OR PREGNANT AT THEIR FINAL 580299/008 STUDY VISIT (VISIT 10 AT MONTH 48).

Associate Professor Rachel Skinner

This study is an extension of the HPV-008 research study with GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine for healthy females 15 – 25 years of age. This study offered women additional gynaecological follow-up if they were shown to have a positive oncogenic HPV infection although their cervical cytology test was normal at their last HPV-008 study visit. In addition, a woman who was pregnant at her last HPV-008 study visit and no cervical sample was taken, was also eligible to enter. Nineteen women were eligible to participate in this study which began in 2009.

Funders of the project - GlaxoSmithKline

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.

Dr Tanya Stoney and Associate Professor Rachel Skinner

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 world wide, 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 ongoing.

Funders of the project - GlaxoSmithKline

A PHASE IIA RANDOMIZED, DOUBLE BLIND, CONTROLLED WITH GARDASIL™ CLINICAL TRIAL TO STUDY THE TOLERABILITY AND IMMUNOGENICITY OF V505 (A MULTIVALENT HUMAN PAPILLOMAVIRUS [HPV] L1 VIRUS-LIKE PARTICLE [VLP] VACCINE) IN HEALTHY 16 TO 26 YEAR OLD WOMEN

Associate Professor Peter Richmond

Currently there are two HPV vaccines available that prevent infection of some HPV types:

1. GARDASIL® a vaccine developed by Merck Sharp & Dohme (Australia) Pty. Ltd. and manufactured by CSL. This vaccine provides protection against HPV types 6, 11, 16 & 18 and is currently available free for girls and women aged 9 to 26 years. GARDASIL® will be used as the 'Control' vaccine in this study.

2. Cervarix*, developed by GlaxoSmithKline, provides protection against the infection of HPV types 16 & 18.

Merck Sharp & Dohme (Australia) Pty. Ltd. has developed a new vaccine called V505 which is designed to protect against 9 different types of HPV infection with are responsible for about 90 per cent of cervical cancers and 90 percent of genital warts. This vaccine is similar to the GARDASIL® in that it contains proteins called VLPs that resemble different types of HPV to the body's immune system, but are not actually viruses. This is the first time this study vaccine (V505) has been tested in humans, however a vaccine with eight (8) of the VLPs has been tested in people and found to be generally well tolerated.

This study has been ongoing since 2007 and 25 subjects were recruited at this site. This study was completed in 2011.

Funders of the project. Merck Sharp and Dohme

A PHASE 1 TRIAL TO EVALUATE THE SAFETY, TOLERABILITY AND IMMUNOGENICITY OF 3 ASCENDING DOSE LEVELS OF A 3- ANTIGEN

STAPHYLOCOCCUS AUREUS VACCINE (SA3AG) IN HEALTHY ADULTS

Associate Professor Peter Richmond

Staphylococcus aureus (Staph) is a bacterium (germ) that inhabits the skin and mucous membranes throughout life. Staph infection can cause pneumonia, skin and wound infections. The success of antibiotics in the prevention and treatment of staph infection has been limited by the rapid and widespread emergence of antibiotic-resistant strains.

The study is evaluating three different dose levels of the study vaccine in healthy adults aged 18 to 85 years. A placebo was given to some participants to obtain safety data.

Data was collected on how well and how soon the vaccine offers protection against Staph infection.

All per protocol visits have been completed. A final study report and the unblinding of treatment groups is expected mid 2012.

Funders of the project. - Wyeth Pharmaceuticals, Inc/Pfizer

IMMUNOGENICITY AND SAFETY OF ACELLULAR PERTUSSIS VACCINE GIVEN AT BIRTH IN HEALTHY INFANTS.

Associate Professor Peter Richmond, Dr Tanya Stoney

Currently, vaccines to protect against Pertussis (whooping cough) are given from 2 months of age, but almost one third of infant hospitalisations for Pertussis occur prior to 2 months.

This study aims to randomly assign a group of newborn infants to birth acellular Pertussis (Pa) vaccine versus current standard practice. Infants will either receive a Pa-containing vaccine at birth and then 6 weeks, four and six months of age or the standard schedule with the first dose given at 6 rather than 8 weeks. Antibody responses in the blood, which are believed to correlate with protection, will be compared at 6 weeks, 10 weeks, 6 months and 8 months of age.

This study aims to show whether earlier vaccination gives better protection from Pertussis at the time when babies are most likely to die from this infection.

This study is also being conducted in Adelaide, Melbourne and Sydney and is funded by the National Health and Medical Research Council (NHMRC).

The 440 babies required nationally were enrolled by the end of February 2012. Our site completed recruitment at the beginning of November 2011.Over half of the babies have completed all the study visits. There have been no serious adverse events causally related to the study vaccine and there have been no concerns with solicited and unsolicited adverse events after subsequent vaccines.

Funders of the Project - MHMRC

A PHASE 3 STUDY TO ASSESS THE IMMUNOGENICITY, SAFETY AND CONSISTENCY OF LOT MANUFACTURE OF ROSS RIVER VIRUS VACCINE IN HEALTHY MALE & FEMALE SUBJECTS 16YRS OF AGE AND OLDER.

Associate Professor Peter Richmond

Ross River virus is a mosquito-borne virus that causes Ross River Virus Disease (RRVD) in humans. Ross River is endemic and enzootic in Australia, Papua New Guinea, adjacent Indonesia and the Solomon Islands. In the past 10 years RRVD has been most prevalent among adults aged 25 and 39 and does not display a clear sex effect.

Subjects were divided into two age strata; Stratum A -1800 subjects aged 16 to 59 yrs and stratum B - 210 subjects aged 60 and over. A subset of approximately 1140 subjects in stratum A and all subject in stratum B were included in the immunogenicity evaluation.

The study involves six clinic visits with three vaccinations and 2 follow phone calls. Those subjects in the immunogenicity group have a blood draws at each visit. Subjects complete diary cards to capture injection site reactions, systemic adverse events and other AE's.

Recruitment for this study commenced in April 2011with 114 subjects recruited at this site. There are a total of six sites in Australia.

Funders of the project - Baxter

A PHASE 1/2A, RANDOMISED, DOUBLE-BLINDED, PLACEBO-CONTROLLED, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY AND VACCINE-LIKE VIRAL SHEDDING OF MEDI-534, A LIVE, ATTENUATED INTRANASAL VACCINE AGAINST RESPIRATORY SYNCYTICAL VIRUS (RSV) AND PARAINFLUENZA VIRUS TYPE 3 (PIV 3), IN HEALTHY 6 - <24 MONTH-OLD CHILDREN IN AND 2 MONTH OLD INFANTS

Assoc/Prof Peter Richmond, Dr Tanya Stoney

RSV and PIV3 are important causes of bronchiolitis (inflammation of the small airways in the lungs) and pneumonia in infants and young children. The purpose of this study is to describe the safety, immune response (ability of the body to fight infection), and virus shedding (virus that can be found in the nose after vaccination) of an experimental live PIV3 and RSV nasal vaccine called MEDI 534 in comparison to a placebo (an inactive sugar and salt solution that does not contain the vaccine, MEDI-534). MEDI -534 or placebo is given as nose drops in this study.

Recruitment for this study was completed in 2011, all subjects have received there last dose of Investigational Product. The study is in phone call follow up of which the last calls will take place in October 2012. The Vaccines Trials Group recruited 4 participants to this study. All visits and phone call follow ups were completed in January 2012.

Funders of the project - MedImmune

A PROSPECTIVE STUDY TO EVALUATE THE IMMUNOGENICITY OF TRIVALENT INACTIVATED INFLUENZA VACCINE IN CHILDREN (≥ 6 MONTHS TO ≤ 18 YEARS OF AGE) WHO ARE ON CANCER THERAPY

Dr Ushma Wadia, Dr Rishi Kotecha, Dr Nick

Gottardo, Dr Angela Alessandri, Prof. Catherine Cole, Assoc/Prof Peter Richmond

Influenza (the Flu) is an easily spread disease caused by a virus, which most commonly causes fever, cough, breathing problems, runny/blocked nose, tiredness or irritability. Young children, elderly, and those on chemotherapy are more likely to be infected, and are more likely to develop serious complications, which may require hospitalisation, and even in rare cases death. Those on cancer therapy should be given the flu vaccination every year. You can still get a cold despite being vaccinated as a result of infection with either a different strain not covered by the vaccine, or not being able to produce protective antibodies to the three stains in the vaccine.

This study recruited 130 participants and the last samples were collected in November 2011. Currently the statistics are being prepared so that an article can be written up for a journal submission. The PHAA 13th National Immunisation conference to be held in Darwin between 19th and 21st June 2012, has accepted our abstract as a poster presentation.

Funders of the project - PMH Foundation Grant

A PHASE 3, RANDOMIZED, COMPARATIVE, MULTICENTER OBSERVER-BLIND STUDY EVALUATING THE SAFETY AND IMMUNOGENICITY OF NOVARTIS RMENB+OMV NZ VACCINE FORMULATED WITH OMV MANUFACTURED AT TWO DIFFERENT SITES, IN HEALTHY ADOLESCENTS AGED 11-17 YEARS

Associate Professor Peter Richmond

The meningococcal B vaccine study was conducted in Australia and internationally to compare 2 batches of the same vaccine manufactured at 2 different sites. The study was conducted to see if the Men B vaccines are safe and effective in adolescents. It is hoped that the vaccines produced at two different manufacturing sites will produce the same antibody responses in the study participants.

The Vaccine Trials Group has enrolled 12 participants into the study. Participants attended Vaccine Trials Group for 3 visits over 2 months. They were vaccinated at visits 1 and 2, and blood sample was collected at visits 1 and 3. A diary card was completed by participants after each vaccination.

The active part of the meningococcal B vaccine study has closed in February 2012 and we are currently waiting for the results.

Funders of the project - Novartis Vaccines and Diagnostics

A PHASE III, OPEN RANDOMIZED, CONTROLLED, MULTI-CENTRE STUDY TO DEMONSTRATE THE NON-INFERIORITY OF THE MENINGOCOCCAL SEROGROUP C AND THE *HAEMOPHILUS INFLUENZA* TYPE B IMMUNE RESPONSE OF GLAXOSMITHKLINE(GSK) BIOLOGICALS' CONJUGATE HIB-MENC VACCINE CO-ADMINISTERED WITH GSK BIOLOGICALS' MEASLES-MUMPS-RUBELLA VACCINE, PRIORIX™, VERSUS MENC-CRM197 CONJUGATE VACCINE CO-ADMINISTERED WITH GSK BIOLOGICALS' HIB VACCINE, HIBERIX™ AND PRIORIX™ IN 12- TO 18-MONTH-OLD TODDLERS PRIMED IN INFANCY WITH A HIB VACCINE BUT NOT WITH A MENINGOCOCCAL SEROGROUP C VACCINE; AND TO EVALUATE THE LONG TERM ANTIBODY PERSISTENCE UP TO 5 YEARS AFTER THE ADMINISTRATION OF THE HIB-MENC VACCINE NO 106445 (PRIMARY PHASE) 106446,106449,106450,106452,106454 (LONG TERM FOLLOW UP)

Associate Professor Peter Richmond

This trial commenced in 2006 with 49 toddlers at this site. The children received either a combined Hib and MenC (HibMenC) vaccine with the MMR vaccine at 12 months of age or the regular scheduled vaccines. The aim of this study is to demonstrate that the combined HibMenC vaccine produces as good as or a better immune response than the same components when given separately.

We are currently completing the final visit in the fifth year of long term follow up for these children. The children have come in for annual visits for blood samples taken to measure their long term immunity to the Hib bacteria. Of the 49 subjects that were initially enrolled, 37 subjects are still involved in this study after 5 years.

Funders of the project - GlaxoSmithKline

MENINGOCOCCAL B VACCINE STUDY IN 11 TO 18 YEAR OLDS: STUDY PROTOCOL 6108A1-2001. WW

Associate Professor Peter Richmond

Pfizer Australia Pty Ltd (formerly Wyeth Australia Pty Ltd) Vaccines Research has developed an investigational vaccine (rLP2086) against Meningococcal B infection. The study commenced at VTG with the first subject visit on 09 February 2009.

Stage 1: Stage 1 was designed to assess the safety and immunogenicity of the Meningococcal B vaccine and to provide the basis for the dose selection for stage 2.

The Meningococcal B vaccine was evaluated at three dose levels (60 micrograms, 120 micrograms, and 200 micrograms, and placebo. VTG enrolled 77 participants in stage 1.

Stage 2: Commenced with the first subject visit on 26 February 2010. Participation in Stage 2 will last up to 3 ½ years. Subjects in cohorts 2, 3 and 4 who received dose levels 120 micrograms, 200 micrograms and placebo were invited to participate in stage 2.

Stage 2 will continue to evaluate the vaccine's ability to produce long term protection to Meningococcal B disease. VTG enrolled 33 participants in stage 2, with no subject withdrawals to date.

Funders of the project - Pfizer Australia Pty Ltd

MENINGOCOCCAL ANTIBODY LEVELS IN

11 – 15 YEARS OLDS WHO RECEIVED A SINGLE 'CATCH UP' DOSE OF MENC VACCINE IN 2003/4

Associate Professor Peter Richmond

This study recruited 240 Australian children and teenagers in Melbourne (160 participants) and Perth (80 participants), aged between 11 and 15 years, who received a single dose of MenC vaccine during a national 'catch-up' campaign in 2003/4.

We want to measure each child's antibodies to MenC, to see if they still have levels thought to be protective. This information is vital to help the Australian Government work out whether an extra dose of MenC vaccine will need to be included in the Australian National Immunisation Program

Funders of the project - Novartis vaccines

Surveillance

THE WESTERN AUSTRALIAN CHILDREN'S FOLLOW UP AND ACTIVE SURVEILLANCE OF TRIVALENT INFLUENZA VACCINE (FAST) STUDY

A/Prof. Peter Richmond, A/Prof. Christopher Blyth, Dr Nicholas Conway, Dr Tracy Markus

To detect any significant increase in seasonal trivalent inactivated influenza vaccine (TIV) related febrile reactions and/or any other adverse events following immunisation (AEFI) with seasonal TIV and to provide active surveillance of seasonal TIV associated adverse events and provide timely feedback to healthcare consumers re: rate of TIV associated adverse events.

In 2011 399 children were recruited. Significant adverse-events including fever following TIV were not observed in children who received the 2011 formulation of Vaxigrip and overall rates of any reaction were low.

Funders of the project - Communicable Disease Control Directorate, Health Protection Group, Western Australian Department of Health (WA DoH)

PAEDIATRIC ACTIVE ENHANCED DISEASE SURVEILLANCE - PAEDS

Associate Professor Peter Richmond, Associate Professor Christopher Blyth

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 four sites involved across Australia:

- Princess Margaret Hospital for Children (PMH), Perth
- Women's and Children's Hospital, Adelaide
- Royal Children's Hospital, Melbourne
- The Children's Hospital at Westmead, NSW

PAEDS objective is to test the value of hospital-based active surveillance for identifying and investigating childhood conditions of public health importance which are difficult to adequately capture through other surveillance mechanisms.

The three conditions currently included as surveillance studies are: Acute Flacid Paralysis (AFP), Intussusception (IS) and Severe Varicella (VZV)

Cases screened and recruited at PMH from 1.1.2011 – 31.12.2011

AFP - 191 cases of AFP screened and 8 recruited with 100% stool sample collection

IS - 918 cases of IS screened and 18 recruited

VZV (Severe hospitalised) - 208 cases screened and 7 recruited

Funders of the project - Commonwealth Dept of Health & Ageing

THE CHILDREN'S WESTERN AUSTRALIAN INFLUENZA VACCINE EFFECTIVENESS (WAIVE) STUDY

Associate Professor Peter Richmond, Associate Professor Dr Christopher Blyth, Dr Dale Carcione, Dr Gabriela Dixon, Dr Paul Effler, Associate Professor Gary Geelhoed, Dr Anthony Keil, Dr Heath Kelly, Dr Alan Leeb, Dr Hannah Moore, Dr David Smith, Dr Paul Van Buynder, Avram Levy, Peter Jacoby

The main objectives of the WIAVE study are:

- To assess the effectiveness of the trivalent influenza vaccine in young children (full and partially vaccinated) and to assess the burden of influenza in young children and their families
- We recruit children aged between 7mths and 5years who present to Princess Margaret Hospital for Children Emergency Department & hospital inpatients with an influenza like illness(ILI)
- During the 2011 influenza season we recruited a total number of 637 subjects. Of these, 517 children presented to the Emergency Department, and 120 were admitted to hospital.
- Even though the recruitment numbers were high for 2011, uptake of the influenza vaccine for under five year olds was very low (15% fully vaccinated for PMH hospital inpatients and only 5% for PMH Emergency Department recruitments). This was likely to be due to the adverse events associated with the CSL Fluvax brand influenza vaccine given in 2010 which caused an increase in high fever and febrile convulsions.
- Of the 633 subjects recruited with nasal swab/PNA results, there were a total of 69 positive Influenza results.

Funders of the project - Communicable Disease Control Directorate, Department of Health WA

ROTAVIRUS AND GASTROENTERITIS SURVEILLANCE STUDY (RAGS)

Associate Professor Peter Richmond, Dr Paul Effler, Dr Dale Carcione, Professor David Forbes, Associate Professor Gary Geelhoed, Dr Gerald Harnett, Dr Anthony Keil, Associate Professor Carl Kirkwood, Professor Tom Riley, Dr David Smith, Dr Michael Watson, Simon Williams

RAGS aims to assess the effectiveness of Rotavirus vaccine on community acquired

Rotavirus presenting to ED and hospital inpatients and also to assess the impact of the infant rotavirus immunisation program on rotavirus genotypes circulating in the community.

We recruit children presenting to the Princess Margaret Hospital for Children (PMH) emergency department or admitted to the medical ward with acute gastroenteritis under the age of 5 years and who have a history of at least 3 episodes of diarrhoea within 24 hour period.

In 2011 there were a total of 52 subjects recruited. Of these 60% of children were vaccinated for Rotavirus. Out of the 48 stool samples collected, only one child tested positive for rotavirus and this child had not received a rotavirus vaccine.

Funders of the project - Department of Health WA

Infectious Disease

NEWBORN INFECTION AND IMMUNITY

Dr Andrew Currie

Preterm infants (>22,000/year in Australia) are particularly prone to infections with commensal microorganisms, such as coagulase negative staphylococci, which rapidly colonise all newborns after birth. Additionally, preterm infants have worse outcomes from infections with more pathogenic organisms such as *Escherichia coli* and *Candida albicans*. As defence against infection in the newborn is critically reliant on the innate immune system, detailed comparison of preterm and term infant responses to various microorganisms will allow characterisation of the key innate responses that normally recognise and control both commensals and pathogens in healthy infants and children. We have established a number of clinical studies which give us unique access to preterm and term infant samples, both at birth (cord blood) and during early life and childhood, when the risk of infection is highest. Using these cohorts we are trying to:

1) Identify critical innate immune pathways of newborn commensal and pathogen recognition

2) Study the development of the innate immune system in infancy and early childhood

3) Examine the impact of antenatal factors (such placental inflammation) on innate immune function

4) Determine if innate responses in the newborn are epigenetically regulated

Funders of the project - Health and Medical Research Council (NHMRC)., BrightSpark Foundation Inc, PMH Foundation, European Society of Infectious Diseases

DYNAMICS OF *HAEMOPHILUS HAEMOLYTICUS* AND NONTYPEABLE *HAEMOPHILUS INFLUENZAE* COLONISATION IN OTITIS-PRONE CHILDREN

Dr Selma Wiertsema and Dr Lea-Ann Kirkham

Ear infections (OM) are predominantly caused by nontypeable *Haemophilus influenzae* (NTHi). Aboriginal children have the highest NTHi OM rates in the world. A vaccine has been introduced to Australia to reduce NTHi carriage and OM. *H. haemolyticus* (Hh) masquerades as NTHi leading to inaccurate surveillance of NTHi carriage.

This project will document true NTHi and Hh carriage rates in OM-prone children, to guide national vaccine policy and set a benchmark for assessing the impact of OM-targeted vaccines in Australian children.

Funder of the project - National Health and Medical Research Council (NHMRC).

EVALUATION OF ANTIBODY LEVELS AND FUNCTION IN OTITIS-PRONE AND HEALTHY AUSTRALIAN CHILDREN

Dr Selma Wiertsema and Dr Lea-Ann Kirkham

We and others have shown that children with ear infections (OM) have a good immune response against the pneumococcus which causes OM, however, these children still get sick. This raises two important questions:

1) is the immune response actually doing what it is meant to do and

2) is the immune system doing this at the right site, i.e. in the middle ear

To answer these questions we will use blood, saliva and middle ear fluid samples that we collected from children with OM. This work will give insight into the role of the immune system in the development of OM and will contribute to advanced prevention and treatment strategies for OM.

Funder of the project - National Health and Medical Research Council (NHMRC).

ROLE OF BACTERIAL BIOFILM AND INTRACELLULAR INFECTION IN CHRONIC AND RECURRENT OTITIS MEDIA

Associate Professor Peter Richmond, H. Coates, S. Vijayasekaran and R. Thornton

While more than 80% of children will experience at least one ear infection (OM) episode by three years of age, 33% will experience three or more episodes by this same age. Increases in children who suffer from recurrent OM have been observed and antibiotic treatment in these children is often ineffective. Our work has shown that the bacteria which cause these infections can be found in a 'slime' or biofilm on the skin in the middle ears of children. When bacteria are in this slime they are seen to be up to 1000 times more resistant to antibiotics than the 'free floating' bacteria which make the children sick. They also allow the bacteria to be shielded from the body's own response meaning that when the antibiotics are finished the bacteria can again become free floating and cause an infection.

We have also shown that as well as been in slime, these bacteria can live inside the cells of the middle ear, the problem with this being that when they survive inside the cell they are again largely protected from the antibiotics that are commonly used to treat this infection

as well as the body's own immune response. Whether is biofilm or intracellularly, these bacteria represent an infectious reservoir from which they can cause reinfection giving rise to what we see in some children who always seem to have glue ear or infections.

These findings are very important as it leads us to explore new treatment options that will hopefully be more effective at targeting these infectious reservoirs and preventing chronic and recurrent infections in the future.

Funder of the project - PMH Seeding grant, Garnett Passe and Rodney Williams Foundation.

DISSOLVING THE GLUE IN GLUE EAR: ASSESSMENT OF THE USE OF DORNASE ALFA AS AN ADJUNCT THERAPY TO VENTILATION TUBE INSERTION.

R. Thornton, P. Richmond, H. Coates, S. Vijayasekaran and P. Jacoby.

Grommet insertions for middle ear infections are the second most common reason for preschool children to undergo surgery. Up to one third of these children will need to have repeat surgeries due to infection recurrence. We believe the recurrence of otitis media is due to the presence of bacteria in "slime" which is known as biofilm. Biofilm protects bacteria from the body's immune responses and makes bacteria up to 1000 times more resistant to antibiotics. These biofilm structures need to be broken down to make treatments work. We have shown that biofilms can be found within DNA net-like structures in the middle ear fluid. These DNA structures are largely produced by cells of the immune system known as neutrophils. This is similar to what is seen in the lung fluid from patients with cystic fibrosis.

We believe that these DNA nets form the "glue" in the middle ear and behave like the sticky fluid in the lungs of children with cystic fibrosis. This stops the body from getting rid of the bacteria and acts as a site where bacteria are able to grow and reinfect the ear. We believe that these DNA nets represent a treatment target to reduce the number of complications and ear infections following grommet surgery. Breaking down this glue will also make the bacteria more susceptible to the body's protective responses.

In the laboratory we have shown that in a test tube, a treatment commonly used in cystic fibrosis treatment (Pulmozyme® or Dornase alfa) is able to break down the sticky "glue" from the ears of children with chronic and recurrent middle ear infections. We believe that this has practical applications in treating middle ear infections and lowering the rate of infection recurrence following grommet insertion.

In this study we will trial the use of Dornase alfa at the time of grommet insertion to break down the "glue" in the middle ear to allow for more effective clearance of bacteria from this site and to increase the effectiveness of the antibiotic drops which are commonly used.

Funders of the project - Western Australian Government State Health Research Advisory Council and PMH Foundation.

MECHANISMS OF BACTERIAL PERSISTENCE AND POTENTIAL FOR VACCINATION IN PATIENTS WITH COPD.

P. Richmond, R. Thornton, S. Wiertsema and L. Kirkham.

Chronic obstructive pulmonary disease (COPD) is a broad term used to describe chronic lung disease that includes bronchiectasis, chronic bronchitis, chronic asthma and emphysema. COPD is the fourth most common global cause of adult death with symptoms including a chronic productive cough, shortness of breath, wheezing and frequent acute infectious exacerbations. Acute exacerbations of COPD have been clearly associated with isolation of respiratory bacteria, particularly nontypeable *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*, from sputa at the time of exacerbation. These recurrent exacerbations result in a worsening of the patient's condition, which usually requires additional treatment and significantly increases mortality rates.

We propose that the cause of recurring bacterial infection in patients with chronic lung disease (COPD) is that bacteria are not cleared from the lung, either by antibiotics or by the host's immune system. We have preliminary evidence that the bacteria survive and persist in the lung in superstructures known as biofilms, which are made up of bacteria surrounded by host and bacterial DNA and proteins. Bacteria residing in a biofilm are resistant to antibiotics and cannot be eliminated by the immune system. When conditions for the bacteria become favourable they can be released from the biofilm and replicate, thereby causing recurring acute infections. This study will confirm whether bacteria survive in biofilms in the lungs of patients with COPD and which species are involved. By understanding how bacteria persist in the lung of these patients we will be able to investigate alternative treatments, such as anti-biofilm agents that allow antibiotics to eradicate the released bacteria. We will also measure the immune response of patients with COPD to investigate whether they are likely to benefit from new and developing protein vaccines that could reduce the incidence of lung infections.

Funder of the project - Westcare.

AN OPEN-LABEL, MULTI-CENTRE, SINGLE ARM STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS ZANAMIVIR IN THE TREATMENT OF HOSPITALISED ADULTS, ADOLESCENTS AND PAEDIATRIC SUBJECTS WITH CONFIRMED INFLUENZA INFECTION

Associate Professor Chris Blyth and Associate Professor Peter Richmond

There are currently no intravenous influenza (flu) antiviral agents approved for use in patients with severe flu. The purpose of this study is to test the safety and effectiveness of a new intravenous form of zanamivir in adults and children with severe flu. Zanamivir is usually given to patients who have the flu, using a puffer. The study commenced in 2010 and due to quieter than usual flu seasons we have not enrolled anyone into the study. The study will be ongoing in 2012.

Funder of the project – GlaxoSmith Kline

Laboratory

GENERIC BANK FOR PERIPHERAL BLOOD MONONUCLEAR CELL (PBMC) AND SERUM TO LOOK AT IMMUNOLOGY RESPONSES TO ALLERGENS, BACTERIA AND VACCINE ANTIGENS

Associate Professor Peter Richmond

This study seeks to establish a bank of peripheral blood mononuclear cells (PBMC's), plasma and serum for the in vitro analysis of adult immunology responses to allergens, bacterial, viral and vaccine antigens. The samples are obtained from healthy volunteers. To date there are 97 study participants enrolled. Throughout the year we replenish stocks of existing participants.

Recruitment is ongoing.

Funders of the Project - Investigator Initiated

PBMC PREPARATION FOR CMI TESTING IN GSK ANTIGEN SPECIFIC CANCER IMMUNOTHERAPEUTIC (ASCI) PROJECTS (NYES01-AS15-MEL-001/112406) OR PERIPHERAL BLOOD MONONUCLEAR CELL PREPARATION FOR CELL MEDIATED IMMUNITY TESTING IN GSK ANTIGEN SPECIFIC CANCER IMMUNOTHERAPEUTIC PROJECTS (NYES01-AS15-MEL-001/112406)

Associate Professor Peter Richmond

Late 2011 the Vaccine Trials Group (VTG) became a certified laboratory for the processing of peripheral blood mononuclear cells (PBMCs) for the GSK Antigen Specific Cancer Immunotherapeutic (ASCI) project NYES01-AS15-MEL-001/112406. This study explores the immune responses and holistic outcomes of immunotherapy on 8 cancer patients. The patients are followed up with 12 visits over a 5 year period. The clinical side to the study takes place at the Princess Alexandra Hospital in Queensland and the Cancer Clinical Trials Centre in Victoria. Blood is then flown to the VTG in Perth for processing where PBMCs are frozen and sent on to GSK for final analysis.

VTG had to meet a variety of 'minimum quality assurance requirements' that GSK set to become a certified lab. In addition to this four laboratory personnel completed a 'dry run' where samples were processed and the PBMCs were sent to GSK for analysis, to determine if the operators and the methods used were adequate for the study. All personnel obtained their certification in November 2011. VTG was ready to receive samples in 2011 however no samples were sent.

Funders of the project: GlaxoSmithKline

Staff and Students

HEAD OF DIVISION

Peter Richmond MB BS MRCP FRACP
Associate Professor, School of Paediatrics and Child Health, University of Western Australia
Consultant Paediatrician and Paediatric Immunologist, Princess Margaret Hospital for Children
Director, Child and Adolescent Health Research Network, Child and Adolescent Health Service
Head, Department of Clinical Research and Education, Child and Adolescent Health Services
Honorary Research Fellow and Director, Vaccine Trials Group, Telethon Institute for Child Health Research
Deputy Chair, Australian Technical Advisory Group on Immunization, Commonwealth Department of Health and Aging

RESEARCH STAFF

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Andrew Currie PhD BSc (Hons)

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Samantha Curtis BSc (Hons)

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Julie Hibbert BSc (Hons) MSc

Jessica Hillwood Medical student

Julia Inman Medical student

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Zakary Snelson Medical student

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Patrick Thornton Medical student

Ruth Thornton PhD BSc (Hons)

Selma Wiertsema PhD MScBSc

Ushma Wadia MBBS

Verity Watt Medical student

Caroline Wharton EN

POSTGRADUATE STUDENTS

Angela Fuery BSc (Hons) PhD Candidate

Stephanie Trend BSc (Hons) PhD Candidate

Janesssa Pickering (Hons) PhD Candidate

Divya Muthiah Honours student

Gemma Mullaney Honours student

Theses passed

R Thornton, PhD University of Western Australia, Biofilm and intracellular infection: Persistence mechanisms of bacterial otopathogens in chronic and recurrent otitis media.

G Mullaney, Hons (1st Class) University of Western Australia, No difference in the functionality of anti-pneumolysin antibodies in the serum of children with and without recurrent otitis media.

Awards

C Blyth, Research Travelling Award, European Society of Clinical Microbiology and Infectious Diseases, 2011

C Blyth, Clinical Teacher of the Year, Princess Margaret Hospital for Children. 2011

R Thornton, H Coates, P Rigby, S Vijayasekaran & P Richmond, Chronic mucosal disease and the role of intracellular infection, biofilm and the pneumococcus. Frontiers 2010: The Art,Science and Future of Otorhinolaryngology. 2010, Melbourne, Victoria, Australia. (Poster Presentation - Best Poster Award)

External Committees

INTERNATIONAL

C Blyth, Vaccines Working Group, International Society of Chemotherapy

C Blyth, Data Safety and Monitoring Board, A study to determine the safety and immunogenicity of 10-valent and 13-valent pneumococcal conjugate vaccines in Papua New Guinean children

NATIONAL

A Currie, Australasian Society for Immunology Special Interest Group for Infection and Immunity (State representative)

C Blyth, Local Organising Committee: WSPID Conference, World Society for Pediatric Infectious Diseases, Melbourne 2011

C Blyth, Local Organising Committee: ASID Conference, Australian Society for Infectious Diseases, Perth 2012

C Blyth, Australian and New Zealand Mycology Interest Group Business Committee, Australasian Society for Infectious Diseases

C Blyth, Australasian Stewardship of Antimicrobials in Paediatrics Group, Australasian and New Zealand Paediatric for Infectious Diseases Group

C Blyth, Data Safety and Monitoring Board, Bronchiectasis Exacerbation Study (BEST)

R Thornton, S Wiertsema, L Kirkham, J Pickering and K Corscadden. OMOZ 2012 Organising Committee.

P Richmond, Chair, ATAGI MMR-Varicella and Herpes Zoster Vaccine Working Party, 2006 – present

P Richmond, Member, ATAGI Pneumococcal Vaccine Working Party, 2007 – present

P Richmond, Member, ATAGI Hib and meningococcal C Vaccine Working Party, 2008 – present

P Richmond, Member, ATAGI H1N1 Influenza Vaccine Working Party, 2009 – present

P Richmond, Member, ATAGI Influenza Vaccine Adverse Event Working Party, 2010 – present

P Richmond, Deputy Chairperson, Australian Technical Advisory Committee on Immunisation (ATAGI), P Richmond, Commonwealth Dept. of Health and Ageing 2010 to present

P Richmond, Member NHMRC Grant Review Panel for Microbiology & Virology (GRP 2E) August 2011

LOCAL

C Blyth, WA Tuberculosis Advisory Council, Health Department of Western Australia

C Blyth, WA Tuberculosis Control Committee Health Department of Western Australia

C Blyth, Infection Control Committee, Princess Margaret Hospital for Children

C Blyth, Safe Design Advisory Committee. New Children's Hospital, Perth

A Currie, Australasian Society for Immunology (WA) Organising Committee

A Curie, PMH Ethics Scientific Advisory Sub-Committee

P Richmond, WA Immunisation Scientific Advisory Group 2006 – present

Invited Presentations

A Currie. "To in utero and beyond" Australasian Society for Immunology. ASM Adelaide, Dec 2011

C Blyth. Combination antifungals in Aspergillosis. Mycology Masterclass V, Hamilton Island 2011

Numerous local presentations to doctors, community groups, medical students etc

R Thornton. Biofilms and intracellular infection in OM and tonsillitis. Interamerican Pediatric Otorhinolaryngology's (IAPO) 7th International Symposium on Pediatric ENT in São Paulo, 18-20 November, 2011. (Invited Speaker - Workshop)

R Thornton, Chronic mucosal disease and the role of intracellular infection and biofilms Interamerican Pediatric Otorhinolaryngology's (IAPO) 7th International Symposium on Pediatric ENT in São Paulo, 18-20 November, 2011. (Invited Speaker)

R Thornton, Why do children have more tonsillar hypertrophy accounting for most tonsillectomy

indications? Interamerican Pediatric Otorhinolaryngology's (IAPO) 7th International Symposium on Pediatric ENT in São Paulo, 18-20 November, 2011. (Invited Speaker)

P Richmond, Impact influenza is having on the ATSI population. Influenza Specialist Group Annual Scientific Meeting, Melbourne, February 2011

P Richmond, Future of Paediatric influenza vaccination in Australia. Influenza Specialist group Annual Scientific Meeting, Melbourne, February 2011

P Richmond, Immunisation and Chronic respiratory Disease: Who should we immunise? Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Perth, WA, April 2011

P Richmond, Dogmas Regarding Natural Immunology of Pneumococcal Carriage: Where are we now? PneumoCarr Workshop Dogmas, Science and New Frontiers - Immunological Determinants of Pneumococcal Carriage. Helsinki, Finland June 2011

P Richmond, Carriage and immune responses to neonatal and early infant pneumococcal conjugate vaccination followed by pneumococcal polysaccharide vaccine booster in Papua New Guinea. PneumoCarr Workshop Dogmas, Science and New Frontiers - Immunological Determinants of Pneumococcal Carriage. Helsinki, Finland June 2011

P Richmond, Pneumococcal vaccination for Adults at High Risk for Pneumococcal Disease. Adult Pneumococcal vaccine workshop, University of NSW, Sydney August 2011.

P Richmond, Studies on the protection of seasonal influenza vaccines against pandemic influenza. 7th Australian Influenza Symposium, Melbourne, October 2011.

P Richmond, Vaccinating children against influenza: where to now? Roundtable discussion. 7th Australian Influenza Symposium, Melbourne, October 2011.

P Richmond, Meningococcal vaccines in use: what have we learned from the introduction of meningococcal conjugate vaccines? Progress towards control of meningococcal disease NCIRS workshop, Melbourne, November 2011.

P Richmond, Impact of influenza: vaccination in young children in Western Australia: the WAIVE study? 7th World Congress of the World Society for Pediatric Infectious diseases, Melbourne, November 2011.

P Richmond, Burden of Invasive Meningococcal Disease: Impact on Public Health. 7th World Congress of the World Society for Pediatric Infectious diseases, Melbourne, November 2011.

P Richmond, Chairperson. The effect of pneumococcal vaccines on disease worldwide: assessing new data, estimating the impact and exploring global opportunities. 7th World Congress of the World Society for Pediatric Infectious diseases, Melbourne, November 2011.

ACTIVE collaborations

A/Prof Ofer Levy, Harvard Medical School, Boston, USA

Dr Donald Davidson, University of Edinburgh, Scotland, UK

Robyn Marsh and Anne Chang, Menzies School of Health Research, Northern Territory, Australia.

Heidi Smith-Vaughan and Michael Binks, Menzies School of Health Research, Northern Territory, Australia.

Kirsty Short, University of Melbourne, Victoria, Australia.

Kim Lema, Australian Institute of Marine Science, Queensland, Australia.

Allan Cripps and Helen Massa, Griffith University, Queensland, Australia.

Phil Thompson, Lung Institute of Western Australia, Australia

PNG Meningitis and Pneumonia Study group: Blyth C, Greenhill A, Kirkham LA, Lehmann D, Duke T, Tanumei J, Hwaihwanje. Collaboration between PMH, UWA, TICHR and PNGIMR

Severe influenza coinfection Study group: Blyth CC, Webb SAR, Kok J, Dwyer DE, van Hal SJ, Foo H, Ginn AN, Kesson AM, Seppelt I, Iredell JR. Collaboration between UWA, PMH, Royal Perth Hospital, University of Sydney, Westmead Hospital, Liverpool Hospital, Children's Hospital at Westmead

Paediatric Active Enhanced Disease Surveilance. Elliot E, McIntyre P, Booy R, McKartney K, Wood N, Snelling T, Buttery J, Crawford N, Gold M, Marshall H, Richmond P, Blyth CC. Collaboration between Collaboration between University of Sydney, Children's Hospital Westmead, Princess Margaret Hospital, University of Western Australia, Royal Children's Hospital Melbourne, University of Melbourne, Women's and Children's Hospital, Adelaide. University of Adelaide.

Australian Encephalitis Study Group: Jones C, Booy R, Elliot E, Durheim D, Marshall H, Dale R, Buttery J, Kesson A, Barton B, Blyth C. Collaboration between University of Sydney, Children's Hospital Westmead, Princess Margaret Hospital, University of Western Australia, Royal Children's Hospital Melbourne, University of Melbourne, University of Adelaide.

Febrile convulsion following influenza Vaccine Study Group: Blyth CC, Currie AJ, Wiertsema SP, Markus T, Conway N, Kirkham LAS, Fuery A, Mascaro F, Geelhoed GC, Richmond PC Armstrong PK, Dowse GK, Effler PV, Carcione D, Scully M, Weeramanthri TS. Collaboration between UWA, TICHR, PMH, CDCD (DoHWA)

Acute lower respiratory tract infection and database linkage: Moore H, Blyth CC, Effler P, Richmond PC, Lehmann D, de Klerk N, Smith DW, Keil AD. Collaboration between UWA, TICHR, PMH, CDCD (DoHWA), PathWest

Australasian Infectious Diseases Physician survey. Ingram P, Blyth C, Murray R, David J, Cheng A. Collaboration between Royal Perth Hospital, UWA, Sir Charles Gardner Hospital, Menzies School of Health Research, Royal Darwin Hospital, Alfred Hospital, Monash

University

WAIVE: Dr Dale Carcione, Dr Gabriela Dixon, Dr Paul Effler (Public Health Physician), A/Prof Gary Geelhoed (Director, Emergency Dept PMH), Dr Anthony Keil (Microbiologist PMH), Dr Heath Kelly (Epidemiologist), Dr Alan Leeb (General Practitioner), Hannah Moore (Epidemiologist), Dr David Smith (Microbiologist QE11), Dr Paul Van Buynder (Public Health Physician), Simon Williams (Microbiologist QE11)

PUBLICATIONS

2011 Publications for annual report (236)

1. Allen KL, Byrne SM, Lampard A, Watson H, Fursland A. Confirmatory factor analysis of the Eating Disorder Examination-Questionnaire (EDE-Q). Eating Behaviors. 2011;12(2):143-151.

2. Allen KL, Fursland A, Raykos B, Steele A, Watson H, Byrne SM. Motivation-focused Treatment for Eating Disorders: A Sequential Trial of Enhanced Cognitive Behaviour Therapy with and without Preceding Motivation-Focused Therapy. European Eating Disorders Review. 2011;online.

3. Allen KL, Fursland A, Watson H, Byrne SM. Eating disorder diagnoses in general practice settings: Comparison with structured clinical interview and self-report questionnaires. Journal of Mental Health. 2011;20(3):270-280.

4. Al-Tamimi M, Gardiner EE, Thom JY, Shen Y, Cooper MN, Hankey GJ, Berndt MC, Baker RI, Andrews RK. Soluble Glycoprotein VI Is Raised in the Plasma of Patients With Acute Ischemic Stroke. Stroke. 2011 Feb;42(2):498-500.

5. Ambrosini GL, O'Sullivan TA, De Klerk NH, Mori TA, Beilin LJ, Oddy WH. Relative validity of adolescent dietary patterns: A comparison of a FFQ and 3d food record. British Journal of Nutrition. 2011;105(4):625-633.

6. Artigas MS, Loth DW, Wain LV, Gharib SA, Obeidat M, Tang W, Zhai G, Zhao JH, Smith AV, Huffman JE, Albrecht E, Jackson CM, Evans DM, Cadby G, Fornage M, Manichaikul A, Lopez LM, Johnson T, Aldrich MC, Aspelund T, Barroso I, Campbell H, Cassano PA, Couper DJ, Eiriksdottir G, Franceschini N, Garcia M, Gieger C, Gislason GK, Grkovic I, Hammond CJ, Hancock DB, Harris TB, Ramasamy A, Heckbert SR, Heliövaara M, Homuth G, Hysi PG, James AL, Jankovic S, Joubert BR, Karrasch S, Klopp N, Koch B, Kritchevsky SB, Launer LJ, Liu Y, Loehr LR, Lohman K, Loos RJF, Lumley T, Al Balushi KA, Ang WQ, Barr RG, Beilby J, Blakey JD, Boban M, Boraska V, Brisman J, Britton JR, Brusselle GG, Cooper C, Curjuric I, Dahgam S, Deary IJ, Ebrahim S, Eijgelsheim M, Francks C, Gaysina D, Granell R, Gu X, Hankinson JL, Hardy R, Harris SE, Henderson J, Henry A, Hingorani AD, Hofman A, Holt PG, Hui J, Hunter ML, Imboden M, Jameson KA, Kerr SM, Kolcic I, Kronenberg F, Liu JZ, Marchini J, McKeever T, Morris AD, Olin AC, Porteous DJ, Postma DS, Rich SS, Ring SM, Rivadeneira F, Rochat T, Sayer AA, Sayers I, Sly PD, Smith GD, Sood A, Starr JM, Uitterlinden AG, Vonk JM, Wannamethee SG, Whincup PH, Wijmenga C, Williams OD, Wong A, Mangino M, Marciante KD, McArdle WL, Meibohm B, Morrison AC, North KE, Omenaas E, Palmer LJ, Pietiläinen KH, Pin I, Polašek O, Pouta A, Psaty BM, Hartikainen AL, Rantanen T, Ripatti S, Rotter JI, Rudan I, Rudnicka AR, Schulz H, Shin SY, Spector TD, Surakka I, Vitart V, Völzke H, Wareham NJ, Warrington NM, Wichmann HE, Wild SH, Wilk JB, Wjst M, Wright AF, Zgaga L, Zemunik T, Pennell CE, Nyberg F, Kuh D, Holloway JW, Boezen HM, Lawlor DA, Morris RW, Probst-Hensch N, Kaprio J, Wilson JF, Hayward C, Kähönen M, Heinrich J, Musk AW, Jarvis DL, Gläser S, Järvelin MR, Ch Stricker BH, Elliott P, O'Connor GT, Strachan DP, London SJ, Hall IP, Gudnason V, Tobin MD. Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. Nature Genetics. 2011;43(11):1082-1090.

7. Ayonrinde OT, Olynyk JK, Beilin LJ, Mori TA, Pennell CE, de Klerk N, Oddy WH, Shipman P, Adams LA. Gender-specific differences in adipose distribution and adipocytokines influence adolescent nonalcoholic fatty liver disease. Hepatology. 2011;53(3):800-809.

8. Bailey HD, Armstrong BK, De Klerk NH, Fritschi L, Attia J, Scott RJ, Smibert E, Milne E. Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukemia. International Journal of Cancer. 2011;129(7):1678-1688.

9. Bailey HD, De Klerk NH, Fritschi L, Attia J, Daubenton JD, Armstrong BK, Milne E. Refuelling of vehicles, the use of wood burners and the risk of acute lymphoblastic leukaemia in childhood. Paediatric and Perinatal Epidemiology. 2011;25(6):528-539.

10. Bailey HD, Milne E, De Klerk NH, Fritschi L, Attia J, Cole C, Armstrong BK. Exposure to house painting and the use of floor treatments and the risk of childhood acute lymphoblastic leukemia. International Journal of Cancer. 2011;128(10):2405-2414.

11. Banerjee B, Ling KM, Sutanto EN, Musk M, Yerkovich ST, Hopkins PMA, Stick SM, Kicic A, Chambers DC. The airway epithelium is a direct source of matrix degrading enzymes in bronchiolitis obliterans syndrome. Journal of Heart and Lung Transplantation. 2011;30(10):1175-1185.

12. Barraza-Villarreal A, Escamilla-Nuñez MC, Hernández-Cadena L, Texcalac-Sangrador JL, Sienra-Monge JJ, Del Río-Navarro BE, Cortez-Lugo M, Sly PD, Romieu I. Elemental carbon exposure and lung function in schoolchildren from Mexico City. European Respiratory Journal. 2011;38(3):548-552.

13. Bell LM, Curran JA, Byrne S, Roby H, Suriano K, Jones TW, Davis EA. High incidence of obesity co-morbidities in young children: A cross-sectional study. Journal of Paediatrics and Child Health. 2011;47(12):911-917.

14. Bertram C, Gottardo NG, Kees UR, Bhoola KD, Dallas P, B. Biological and Clinical Relevance of Neural Stem Cells in the Pathogenesis of Childhood Medulloblastoma. In: Salvatti EK, editor. Brain Cancer, Tumor Targeting and Cervical Cancer. New York: Nova Science; 2011. 75-162.

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16. Blair E. Rates of cerebral palsy. In: P. PC, editor. Cerebral Palsy - A multidisciplinary approach. Munich-Orlando: Dustri-Verlag Dr. Karl Feistle; 2011. 27-37.

17. Blair E, Cans C, Pantedialis CP. The definition of cerebral palsy. In: P. PC, editor. Cerebral Palsy - A Multidisciplinary Approach. Munich-Orlando: Dustri-Verlag Dr. Karl Feistle; 2011. 13-15.

18. Blair E, de Groot J, Nelson KB. Placental infarction identified by macroscopic examination and risk of cerebral palsy in infants at 35 weeks of gestational age and over. American Journal of Obstetrics and Gynecology. 2011 2011-Aug;205(2):124.e1-124.e7.

19. Blair EM, Nelson KB. Migraine and preterm birth. Journal of Perinatology. 2011;31(6):434-439.

20. Blank F, Stumbles P, Von Garnier C. Opportunities and challenges of the pulmonary route for vaccination. Expert Opinion on Drug Delivery. 2011;8(5):547-563.

21. Blyth CC, Currie AJ, Wiertsema SP, Conway

N, Kirkham LAS, Fuery A, Mascaro F, Geelhoed GC, Richmond PC. Trivalent influenza vaccine and febrile adverse events in australia, 2010: Clinical features and potential mechanisms. Vaccine. 2011;29(32):5107-5113.

22. Blyth CC, Markus TY, Effler PV, Richmond PC. Ensuring safety of the 2011 trivalent influenza vaccine in young children. Medical Journal of Australia. 2011;195(1):52.

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